BLOOD

Blood Cells

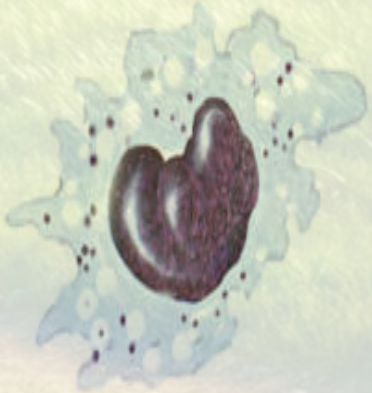
Monocyte

Lymphocyte

Neutrophil

Eosinophil

Basophil



Macrophage

Erythrocyte

Platelets

INDEX

BONE MARROW

- It is a spongy material in the centre of some of our bones.
- It produces cells known as stem cells.

STEM CELLS

- Immature cells that develop into 3 different types of blood cells.

BLOOD CELLS

- **Red blood cells:** carry oxygen to all cells in the body.
- **White blood cells:** fight infections and form part of our immune system.
- **Platelets:** help the blood to clot, to prevent bleeding.

NORMAL BLOOD VALUES

A) RED BLOOD CELLS

1. Red cell count:

nearly 5 millions / cmm

- In females: 4.5 – 5 millions — In males: 5 – 5.5 millions.
- Increase = polycythemia — Decrease = anemia.

2. Hemoglobin concentration:

nearly 15 gm %

- In females: 12 – 16 gm % — In males: 13 – 17 gm %.
- Increase = polycythemia — Decrease = anemia.

3. Hematocrit value OR Packed cell volume (PCV):

- It is the volume of packed red cells in 100 ml of blood.
- In females: 36 – 48 % — In males: 40 – 52 %.
- Increase = polycythemia — Decrease = anemia.

4. Red cell indices:

a) Mean Cell Volume (MCV):

- It is nearly 90 CM.
- In anemia: if MCV < 80 → microcytic anemia.
  if MCV 80 – 100 → normocytic anemia.
  if MCV > 100 → macrocytic anemia.

b) Mean Cell Hemoglobin Concentration (MCHC):

- It is the average hemoglobin concentration in the red cells.
- It is nearly 34 gm / dl.
- In anemia: if MCHC < 30 → hypochromic anemia.
  if MCHC 30 – 35 → normochromic anemia.
  if MCHC > 35 → hyperchromic anemia.

5. Reticulocyte count: (normally: 0.5 – 1.5 %)

- **Reticulocyte:** a young immature RBC newly released from the BM.
- **Reticulocyte count:** reflects the rate of RBC production in the BM.
- **Reticulocytosis:** ↑ reticulocyte count occurs in cases of over active BM:
  - *Hemolytic anemia.*
  - *Acute hemorrhage.*
  - *Anemia under ttt.*
  - *Recovery from BM suppression.*
- **Reticulocytopenia:** ↓ reticulocyte count occurs in cases of suppressed BM:
  - *Aplastic anemia.*

6. Red cell diameter:

- The Mean Cell Diameter (MCD) is 7.2 Microns.
- Microcytosis = less than 7.2 Microns.
- Macrocytosis = more than 7.2 Microns.
- Anisocytosis = variations in size.

7. Red cell morphology:

- Normal red cell: *Biconcave disc.*
- Abnormal red cell:
  - *Schistocytes:* *Traumatic hemolysis.*
  - *Sickle cells:* *Sickle cell anemia.*
  - *Spherocytes:* *Hereditary Spherocytosis.*
  - *Target cells:* *Thalassemia.*
  - *Teardrop RBCs:* *Idiopathic myelofibrosis.*
  - *Howell-Jolly bodies:* *Hyposplenism.*
  - *Poikilocytosis:* *Variable shapes.*

B) WHITE BLOOD CELLS

1. Total leukocytic count (TLC):

4,000 – 11,000 / cmm.

- Increase = leukocytosis

Decrease = leukopenia.

2. Differential leukocytic count:

- Neutrophils: 50 – 70 % (Staff : Segmented = 1 : 10)
- Eosinophils: 2 – 5 %.
- Basophils: 0 – 1 %.
- Lymphocytes: 20 – 40 %.
- Monocytes: 2 – 8 %.

Differential neutrophil count

- Shift to the left: ↑ Staff in overactive BM (bacterial infections).
- Shift to the right: ↑ Segmented in delayed BM (megaloblastic anemia).

Neutrophilia (> 7500 / cmm)

a) Physiological: exercise, emotional stress, pregnancy.

b) Pathological:

- **INFECTIONS** especially BACTERIAL INFECTIONS.
- **INFLAMMATIONS** e.g. collagen diseases as *SLE & RA*.
- **I**atrogenic: e.g. corticosteroids.
- **H**emorrhage.
- **H**emolysis.
- **T**rauma & burns.
- **T**issue injury: e.g. myocardial infarction.
- **M**alignancy: e.g. carcinoma, or blood malignancies.
- **M**etabolic: e.g. DKA, uremia.

Neutropenia (< 2000 / cmm) = Agranulocytosis = Granulocytopenia

1. **Bone marrow aplasia**: see " aplastic anemia ".
2. **Bone marrow infiltration**.
3. Immunological: autoimmune diseases.
4. Infections: Viral infections, TB, Typhoid.
5. Megaloblastic anemia.
6. Hypersplenism.

Eosinophilia

1. **Allergic** disorders: Bronchial asthma, allergic rhinitis, urticaria.
2. **Parasitic** infestations: Toxocara, Schistosoma, Filaria, Ankylostoma.
3. Skin diseases: Allergy, Psoriasis.
4. Immune: PAN, RA.
5. Malignancy: Eosinophilic leukemia, Hodgkin's disease.
6. Miscellaneous: Loeffler's syndrome, Addison's disease.

Eosinopenia

1. **A**cute infections.
2. **B**urns.
3. **C**ushing's syndrome, **C**orticosteroid therapy.

Basophilia

1. **M**alignancies of the blood: e.g. *leukemia*.
2. **M**yxoedema.

Basopenia

1. Allergy.
2. Corticosteroid therapy.
3. Hyperthyroidism.

Lymphocytosis

1. Acute **VIRAL** infections: *Hepatitis, HSV, IMN, CMV.*
2. Chronic BACTERIAL infections: **TB**, Brucellosis, Syphilis.
3. Lymphomas: especially Lymphocytic lymphomas.
4. Lymphatic leukemias: acute & chronic.

Lymphopenia

1. Immunodeficiency diseases.
2. DRUGS: Immunosuppressive drugs & **Corticosteroids**.
3. Lymphomas: especially Hodgkin's disease.
4. Cushing's syndrome.
5. Malnutrition & Malabsorption.

Monocytosis

1. Infections: Brucellosis, Typhoid, TB, Syphilis, SBE, **IMN**.
2. Malignancy: Monocytic leukemias, Hodgkin's disease.
3. Miscellaneous: Collagen diseases, Sarcoidosis.

Monocytopenia

1. Aplastic anemia.
2. Infections: HIV.
3. Immune: SLE.
4. Malignancy: CLL.

C) PLATELET COUNT

- Normally: 150,000 – 400,000 / cmm.

ANEMIA

DEFINITION

1. Reduction in:
   - Red cell count
   - Hemoglobin concentration
   - Hematocrit value

   → Reduction of the O_2 carrying capacity of the blood.

THEREFORE:

2. Reduction in:
   - O_2 delivery to the tissues.

COMPENSATORY MECHANISMS IN ANEMIA

Several compensatory mechanisms occur to maintain tissue oxygenation:

1. ***Increased O_2 delivery to the tissues:*** ***through***
   - Increased cardiac output.
   - Peripheral vasodilatation.
   - Reduced affinity of Hb to O_2.
2. ***Increased erythropoietin production:*** to ↑ red cell production in the BM.
3. ***Increased plasma volume:*** to maintain the total blood volume normal.

FACTORS AFFECTING THE SYMPTOMS OF ANEMIA

1. ***Speed of onset:***
   - Rapidly progressive anemia causes more symptoms than anemia of slow onset, because there is less time for compensatory mechanisms to occur.
2. ***Severity of anemia:***
   - Mild anemia may be asymptomatic.
3. ***Senility:***
   - Symptoms are more severe in the elderly due to:
     impaired cardiovascular compensatory mechanisms in the elderly.

CLASSIFICATION

I. ETIOLOGICAL CLASSIFICATION

A) Decreased red cell production:

1. Decreased proliferation (Hypoproliferative anemia)
   - Aplastic anemia.
   - Myelophthisic anemia.
   - Anemia with organ *failure:*
     - *Renal failure, liver failure, endocrinal failure.*

2. Decreased maturation (Dyshematopoietic anemia)
   - Iron deficiency anemia.
   - Megaloblastic anemia: *B12 or folic acid deficiency.*
   - MDS.

B) Increased red cell destruction:

- Hemolytic anemias.

C) Increased red cell loss:

- Acute post – hemorrhagic anemia.

II. MORPHOLOGICAL CLASSIFICATION

A) Microcytic hypochromic anemia:

1. Iron deficiency anemia.
2. Thalassemia.
3. Sideroblastic anemia.
4. Anemia of chronic disease (ACD).

B) Normocytic normochromic anemia:

1. Aplastic anemia.
2. Myelophthisic anemia.
3. Anemia with organ *failure*.
4. Hemolytic anemia.
5. Acute post-hemorrhagic anemia.
6. Anemia of chronic disease (ACD).

C) Macrocytic anemia:

1. Megaloblastic anemia: *B12 or folic acid deficiency*.
2. Miscellaneous: *Alcohol, liver failure, reticulocytosis, Myxoedema, MDS.*

MANIFESTATIONS OF ANEMIA

I. GENERAL MANIFESTATIONS OF ANEMIA

Symptoms

1. General:
   - Easy fatigue, lassitude, stunted growth *in children with chronic severe anemia.*
2. CVS:
   - Palpitation, exertional dyspnea.
   - Precipitation of angina, precipitation of HF (high cardiac output HF).
   - Intermittent claudications in severe cases.
3. Neurological:
   - Headache, dizziness, blurring of vision, syncope.
   - Lack of concentration.
   - Numbness & tingling: of feet & hands.
4. Genital:
   - FEMALE: Menstrual irregularities, MALE: impotence.

Signs

1. Pallor: best detected in: ***mm of mouth & conjunctiva, palmar creases, nail folds.***
2. Hyperdynamic circulation:
   - Pulse: Tachycardia & big pulse volume.
   - Heart: Accentuated heart sounds, S3, hemic murmurs.
   - In severe cases: High cardiac output HF.
3. Oedema of LL: may occur due to:
   - Hypoxia: which increases the capillary permeability.
   - Salt & water retention.
   - Anemic HF.

II. SPECIFIC MANIFESTATIONS OF ANEMIA

- These are manifestations related to the specific cause of anemia " see later ".

IRON DEFICIENCY ANEMIA

DEFINITION

- **Iron deficiency** is defined as: *a decreased total iron body content.*
- **Iron deficiency anemia** occurs when: *iron deficiency is sufficiently severe to diminish erythropoiesis and therefore cause the development of anemia.*
- **It is the most common type of anemia.**

ETIOLOGY

1. Decreased intake of iron:

- Infants: because iron content of milk is low.
- Elderly: and poor people.

2. Decreased absorption of iron:

- Achlorhydria: e.g. *atrophic gastritis, gastrectomy, cancer stomach.*
- Diet: ↑↑ phosphate & phytate (cereals) or tannate (tea) or oxalates.
- Pica: Ingestion of unusual substances such as clay → ↓↓ iron absorption.
- MALABSORPTION SYNDROME.

3. Increased demand for iron:

- Females in child-bearing period: pregnancy & lactation.
- Growth periods: infancy & adolescence.

4. INCREASED LOSS OF IRON: *(CHRONIC BLOOD LOSS)*

- **GIT:**
  - Oesophagus: varices, **tumours**.
  - Stomach: peptic ulcer, **tumours**.
  - Intestine: Ancylostoma infestation, Angiodysplasia, IBD, piles, **tumours**.

Iron deficiency in an adult male means GIT blood loss until proven otherwise

- Recurrent bleeding: *epistaxis, hematuria, bleeding from wounds, menorrhagia.*
- Repeated blood donation.
- Hemorrhagic blood diseases.
- Hemoglobinuria.

CLINICAL PICTURE

1. General manifestations of anemia: " see before ".

2. Manifestations of iron deficiency:

- ***Mouth:*** Angular stomatitis (Cheilosis).
- ***Tongue:*** Atrophy of tongue papillae.
- ***Nose:*** Atrophy of nasal mucosa + bad smelling discharge (**Ozena**).
- ***Appetite:*** Perverted appetite (**Pica**).
- ***Nails:*** Brittle, flattened, loss of luster + spooning (**Koilonychia**).
- ***Spleen:*** Mild splenomegaly (in 10 % of the cases).

3. Manifestations of specific types of iron deficiency:

A) ANCYLOSTOMA ANEMIA:

- Loss of iron: Features of iron deficiency anemia including Pica.
- Loss of proteins: Hypoalbuminemia.
- Abdominal pain, Alternating diarrhoea & constipation.
- Blood: Eosinophilia.
- Stools: Ancylostoma ova.

B) PLUMMER – VINSON SYNDROME:

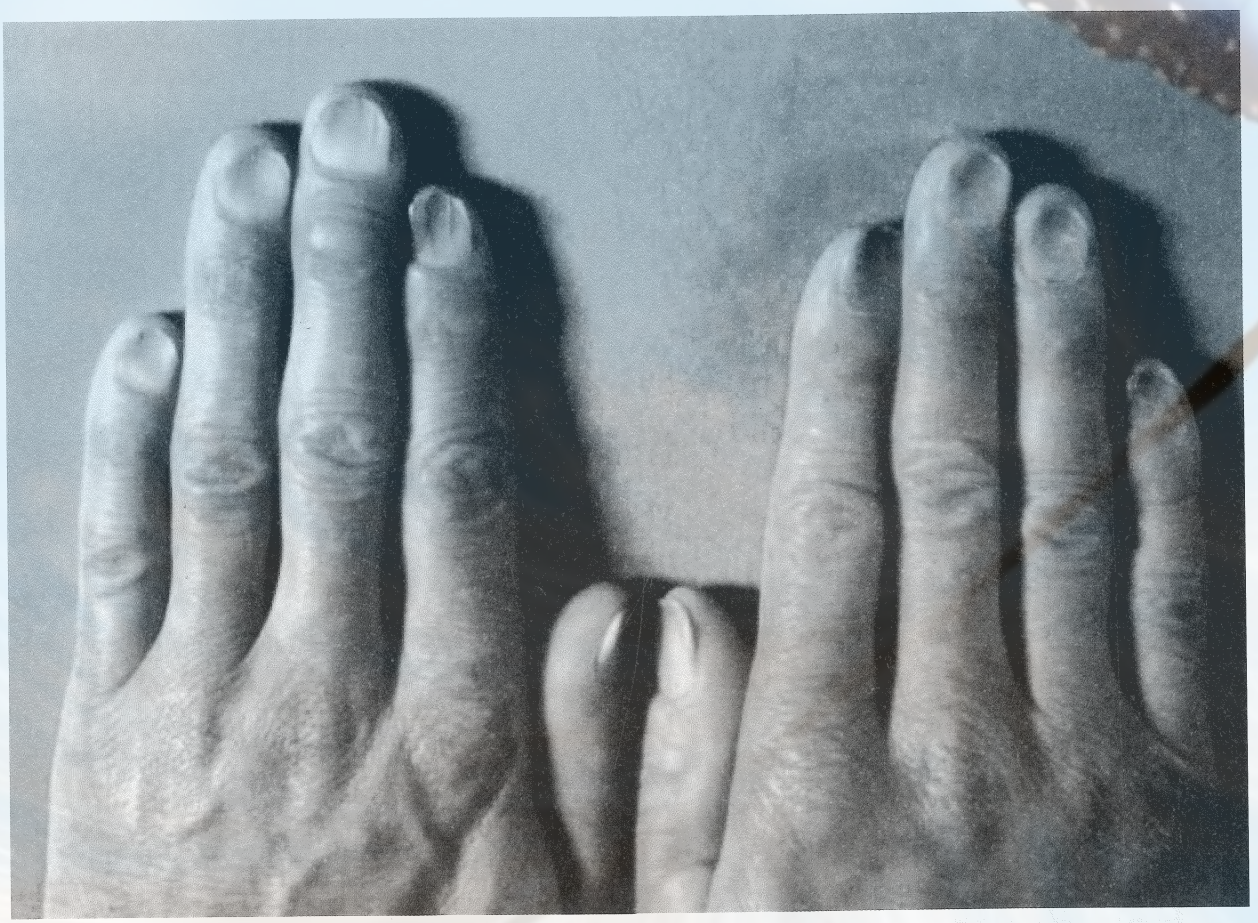
(Paterson – Kelly Syndrome)

- Incidence: usually occurs in middle aged females.
- Features of iron deficiency anemia: especially,

  ***S**tomatitis*, ***S**pooning*, ***S**plenomegaly*.

- DYSPHAGIA: due to oesophageal web (desquamating epithelial cells), which:
  - may obstruct the oesophagus.
  - may be complicated by: post-cricoid carcinoma.
  - may appear in Ba swallow as a: post-cricoid web.

Koilonychia " Iron deficiency anemia "



INVESTIGATIONS

I. For diagnosis of iron deficiency anemia:

1. CBC: *" Features of microcytic hypochromic anemia "*

RBCs:

- Decreased: Red cell count, Hemoglobin level, Hematocrit value.
- Decreased: MCV & MCHC.

WBCs:

- Usually normal.
- Eosinophilia is present in Ancylostoma infestation.

Platelets:

- Usually normal.

2. Bone marrow examination:

- Erythroid hyperplasia.
- Decreased iron stores in macrophages.

3. Evidence of iron deficiency:

- Serum iron, ferritin, transferrin saturation: decreased.
- TIBC: increased.
- FEP: increased.

II. For diagnosis of the cause:

1. Stool examination:

- For occult blood (precautions).
- For Ancylostoma ova.

2. Investigations for GIT hemorrhage:

- Endoscopies: *oesophagoscopy gastroduodenoscopy, colonoscopy.*
- Barium studies: *Ba swallow, Ba meal, Ba enema.*
- Angiography: *is useful in cases of rapid bleeding.*
- RADIO-ISOTOPE BLEEDING SCAN:
  - *Radio-isotope scanning of the abdomen after IV injection of **Technetium** is useful when active bleeding is **too slow** to be detected by angiography.*

3. Investigations for hemostatic disorders:

- See later.

4. Investigations for malabsorption syndrome:

- Refer to GIT.

5. Gastric function tests:

- To detect achlorhydria.

DIFFERENTIAL DIAGNOSIS

- Causes of: Microcytic anemia:

1. Iron deficiency anemia.
2. *Thalassemia.*
3. *Sideroblastic anemia.*
4. *Anemia of chronic disease (ACD).*

TREATMENT

I. Specific TTT

A) TTT of the underlying cause: e.g. ttt of Ancylostoma infestation.

B) Replacement therapy:

- AIM

1. To correct anemia: i.e. to restore the normal Hb level.
   (Hb ↑ about 1 gm % weekly until normal levels are restored)
   (Reticulocyte count begins to ↑ within ***5 days*** of starting ttt)

   Causes of impaired response:
   - *Presence of persistent blood loss.*
   - *Associated ↓ in Hb synthesis.*
   - *Noncompliance to ttt.*

2. To replenish the iron stores: i.e. to provide stores of at least $^1/_2$ to 1 gm of iron.
   (Continous ttt for ***6 months*** after correction of anemia will achieve this)

- METHODS

1. ***Iron – rich diet:***
   - Meats: beef, chicken, fish.
   - Vegetables: leafy greens, legumes, peas, etc….
   - Others: pasta, rice, yeast.

2. ***Iron preparations:***

   a) **Oral iron:**
   - Preparations: *ferrous sulphate, ferrous gluconate, ferrous fumarate.*
   - Dose: 300 mg tds.
   - Side effects:
     - GIT irritation: *anorexia, nausea, vomiting, abdominal pain, constipation.*
     - Dark stools.

   b) **Parentral iron:**
   - Preparations: Iron dextran (IV), or Iron sorbitol (IM).
   - Dose: 100 mg / day IV or IM.
   - Side effects:
     - Local: pain, inflammation, abscess formation, thrombosis.
     - General: **f**ever, **f**lushing, **h**eadache, **h**ypotension, **a**rthralgia, **a**naphylaxis.
   - Indications:
     - Intolerance of oral iron.
     - Malabsorption syndrome.
     - Rapid iron loss.
     - GIT disorders that may be aggravated by oral iron:
       e.g. *peptic ulcer*, *IBD*.

II. Transfusion therapy:

- ***Packed red cell transfusion*** may be needed in cases of severe anemia:
  - Hemoglobin: < 7 gm %.
  - Marked symptoms of anemia.
  - Anemic HF.

III. Symptomatic TTT:

- e.g. ttt of anemic HF.

HEMOLYTIC ANEMIA

DEFINITION

- It occurs due to: premature destruction of the RBCs → short life span of RBCs.
- It occurs when: BM activity cannot compensate for the destroyed RBCs.
- Hemolysis may be: ***intravascular*** *or* ***extravascular***.

ETIOLOGY

I. CORPUSCULAR CAUSES

1. Membrane defects:
   - Hereditary spherocytosis (HS).
   - Paroxysmal nocturnal hemoglobinuria (PNH).
2. Hemoglobin defects: " Hemoglobinopathies "
   - Thalassemias.
   - Sickle cell anemia.
   - Rare types: *Hb C*, *Hb D*, *Hb E*.
3. Enzyme defects:
   - Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency).

ALL the corpuscular causes are HEREDITARY except: PNH.

II. EXTRA-CORPUSCULAR CAUSES

1. Immune hemolytic anemia:
   - Allo-immune: incompatible blood transfusion.
   - Auto-immune: autoimmune hemolytic anemia.
2. Infections:
   - Malaria, Clostridium welchii.
3. Physical:
   - March hemoglobinuria.
   - MicroAngiopathic Hemolytic Anemia: *DIC*, *HUS*, *TTP*.
   - Prosthetic cardiac valves.
4. Chemical:
   - Drugs: *Amphotericin B*.
   - Toxins: *lead, copper, snake venom, RENAL FAILURE.*
5. Hypersplenism.
6. Metabolic: *Wilson's disease*.

CLINICAL PICTURE

1. **General manifestations of anemia:** " see before ".
2. **General manifestations of hemolytic jaundice:**
   - Jaundice: MILD.
   - Stools: DARK.
   - Urine: NORMAL in colour: but darkens on standing.
3. **Hepatosplenomegaly:** is usually present.
4. **Gall stones & intrahepatic biliary obstruction:**
   - May occur due to ↑↑ bile pigment production & will lead to: **OJ**.
5. **Leg ulcers surrounded by pigmentation:**
   - May occur due to ↑↑ iron deposition under the skin.
6. **Different types of crises:**

Hemolytic crisis:

- **P**recipitating factor: **Infections → hyperplasia of the RES.**
- **P**allor: **Marked pallor + deepening of jaundice + dark urine due to hemoglobinuria.**
- **P**yrexia: **Fever & rigors due to pyrogens released from the RBCs.**
- **P**ain: **Generalized bone pains (due to hyperactive BM) + acute abdominal pain.**
- Associated with: **Increased reticulocytic count.**

Aplastic crisis:

- **P**recipitating factor: **Viral infections → BM inhibition → no compensation for destroyed RBCs.**
- **P**allor: **Marked pallor, BUT: no deepening of jaundice & no dark urine.**
- Associated with: **Decreased reticulocytic count.**

Megaloblastic crisis:

- Aggravation of anemia due to: relative folate deficiency.

Sequestrational crisis:

- Aggravation of anemia due to: pooling of the RBCs in the spleen.

Vaso-occlusive crisis:

- Painful occlusion of the blood vessels: in sickle cell anemia only.

7. **Manifestations of the cause:** e.g.
   - In PNH: Iron deficiency.
   - In Thalassemia: Iron overload.
   - In Sickle cell anemia: Vascular occlusion.

INVESTIGATIONS

I. Diagnosis of hemolytic anemia:

1. CBC:

RBCs

- Normocytic normochromic anemia: with normal MCV & normal MCHC.
- Macrocytic anemia may occur: in ***megaloblastic crisis*** or in ***severe reticulocytosis***.
- Microcytic anemia may occur: in case of thalassemia.
- Reticulocytic count: High , is the rule... Low in aplastic crisis.
- Blood film: may reveal characteristic red cells, e.g. *sickle cells*.

WBCs & Platelets

- Usually normal: BUT may ↑ due to hyperactive BM.

2. Bone marrow examination:

- Hyperplastic BM: this is the rule.
- Hypoplastic BM: in aplastic crisis.
- Megaloblastic BM: in megaloblastic crisis.

3. Measure of life span of RBCs: " *using Cr – labelled red cells* "

- Shortened life span of RBCs.

4. Bile pigments:

- Serum bilirubin: increased mainly the indirect.
- Stools: increased stercobilinogen.
- Urine: increased urobilinogen, *absent bilirubin*.

5. Serum LDH: increased.

II. Differentiating Intravascular & Extravascular hemolysis:

- Laboratory features of Intravascular hemolysis:
  - **H**emoglobin*uria*.
  - **H**emosiderin*uria*.
  - **H**aptoglobin: *is markedly decreased in plasma.*
  - **H**emopexin: *is markedly decreased in plasma.*

III. For diagnosis of the cause: e.g.

- In PNH: Flow cytometry.
- In Thalassemia: Hemoglobin electrophoresis.
- In Sickle cell anemia: Hemoglobin electrophoresis.

HEREDITARY SPHEROCYTOSIS

ETIOLOGY

- Hereditary deficiency of a protein in the **MEMBRANE** of the RBCs leading to:
  - RBCs become rigid (less deformable) → destruction especially in the *spleen*.
  - RBCs become more permeable to water → ↑↑ **OSMOTIC FRAGILITY**.
  - RBCs become small & spherical → ***microspherocytes***.

CLINICAL PICTURE

1. GENERAL MANIFESTATIONS OF: HEMOLYTIC ANEMIA.
2. *Family history:* *is usually positive.*
3. *Onset:* *is usually during childhood.*

INVESTIGATIONS

1. GENERAL INVESTIGATIONS OF: HEMOLYTIC ANEMIA.
2. Osmotic fragility test: ↑↑ **OSMOTIC FRAGILITY** of the RBCs.
3. Blood film: ***microspherocytes.***

TREATMENT

1. Splenectomy: prolongs the life span of the RBCs.
2. Transfusion therapy: " see before ".

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

ETIOLOGY

" **UNKNOWN** "

- Acquired mutation of BM stem cells → production of cells with abnormal **MEMBRANE**:

- Absence of certain surface proteins (**CD55 & CD59**) from cell membrane of all blood cells; this will render the blood cells abnormally affected by the **COMPLEMENT SYSTEM**:
  1. RBCs: ↑↑ sensitivity to damage by complement → **H**emolytic anemia.
  2. Platelets: ↑↑ platelet aggregation by complement → **H**ypercoagulability & Thrombosis.

- Associated BM hypoplasia may lead to:
  1. RBCs: Decreased production → aggravation of ***anemia***.
  2. Platelets: Decreased production → ***thrombocytopenia***.
  3. WBCs: Decreased production → ***leukopenia***.

} **Pancytopenia**

CLINICAL PICTURE

1. GENERAL: Manifestations of Hemolytic anemia.
2. HEMOLYSIS: **INTRAVASCULAR** with Hemoglobinuria (dark urine especially by night).
3. PAIN: Attacks of abdominal pain & back pain due to ischemia from microthrombi.
4. INFECTION: ↑↑ incidence of infection.
5. **Complications**:
   - *Iron deficiency:* *due to hemosiderinuria & may aggravate the anemia.*
   - *Aplastic anemia:* *and Acute myeloid leukemia.*
   - *Thrombosis.*
   - PANCYTOPENIA.

INVESTIGATIONS

1. General investigations of: **Hemolytic anemia**.
2. Investigations of: **INTRAVASCULAR** HEMOLYSIS.
3. Investigations specific for: **PNH:**
   a) *Activation of complement in the presence of RBCs* → *Hemolysis of RBCs, using:*
      - Ham test: acidification of serum.
      - Sucrose lysis test: adding sucrose to the serum.

   b) ***Flow cytometry:*** *to demonstrate absent surface proteins on RBCs & WBCs:*
      - CD55: DAF (Decay – Accelerating Factor).
      - CD59.

TREATMENT

1. **Symptomatic TTT**:
   - Anemia: **A**ndrogens, *Iron, Transfusion therapy.*
   - Pain: **A**nalgesics.
   - Thrombosis: **A**nticoagulants.
   - Infection: **A**ntibiotics.
2. **Corticosteroids:** prednisone 1 mg / Kg / day.
3. **BMT**.

HEMOGLOBINOPATHIES

- ***Normally:*** Hemoglobin is composed of:
  - Haem: iron-protoporphyrin complex.
  - Globin: protein consisting of 4 polypeptide chains.
- ***Normally:*** Hemoglobin in the adult is of 3 types:
  - Hb A (97 %): its globin is composed of: 2 alpha & 2 ßeta polypeptide chains.
  - Hb A2 (1-2 %): its globin is composed of: 2 alpha & 2 delta polypeptide chains.
  - Hb F (1-2 %): its globin is composed of: 2 alpha & 2 gamma polypeptide chains, and it is the normal Hb in the fetus & diminishes after birth.
- ***In Hemoglobinopaties:***

  There are abnormalities in the structure of the globin molecule → abnormal types of Hb.

THALASSEMIAS

- Hereditary disorders of many types: the most important are alpha & ßeta thalassemia.

Alpha Thalassemias:

- There is ↓↓ production of alpha chains leading to production of Hb H (4 ßeta) & Hb Bart (4 gamma).
- There is a ***homozygous form*** (incompatible with life) & a ***heterozygous form*** (slight anemia).

ßeta Thalassemias:

- There is ↓↓ production of ßeta chains which are replaced by:

  gamma chains → production of: *Hb F*.

  Delta chains → production of: **Hb A2**.
- There are 3 types:
  1. **Thalassemia major:** (Homozygous) = Mediterranean anemia
     - Hb A is markedly reduced: while Hb F is markedly increased (> 80 – 90 %).
     - It presents in adults as: **Mediterranean anemia** or **Cooley's anemia.**
  2. **Thalassemia minor:** (Heterozygous) = Thalassemia trait
     - Hb A is slightly reduced: with ↑↑ in both Hb F (5-10%) & Hb A2 (5-10 %).
     - It presents in adults by: mild microcytic hypochromic **anemia, splenomegaly.**
     - It usually needs no ttt.
  3. **Thalassemia intermedia:**
     - Hb A is variable: it presents with moderate anemia.

Thalassemia Major
Cooley's anemia
Mediterranean anemia

CLINICAL PICTURE

1. GENERAL MANIFESTATIONS OF: HEMOLYTIC ANEMIA.
2. *Family history:* *is usually positive.*
3. *Onset:* *is usually during childhood.*
4. OTHER MANIFESTATIONS:
   - Iron overload: e.g. *Liver cirrhosis, skin pigmentation, diabetes, CM.*
   - Morphological features: e.g. *Mongoloid facies, stunted growth, bone deformities.*

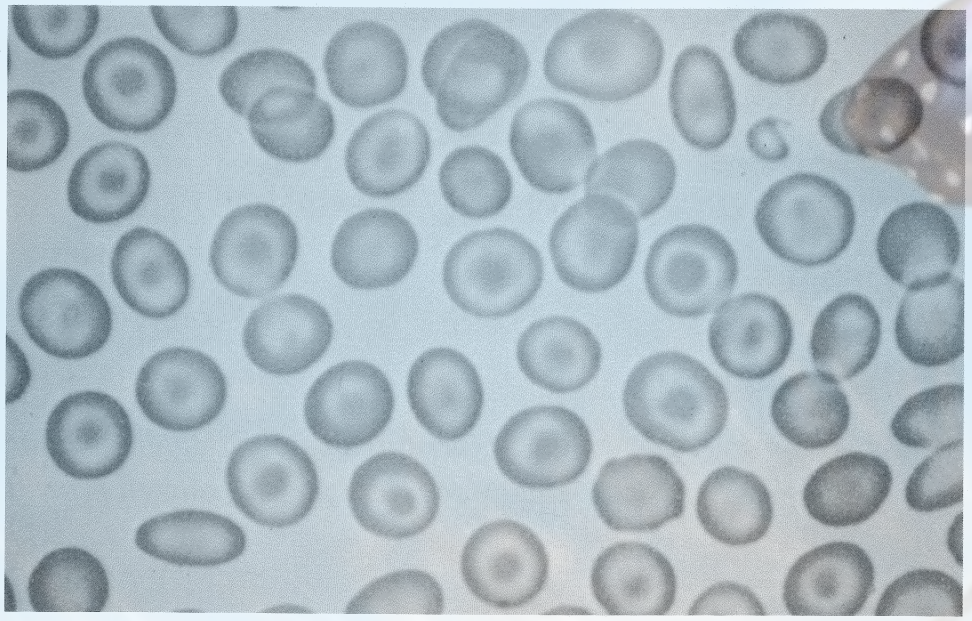
INVESTIGATIONS

1. General investigations of: **Hemolytic anemia**.
2. Investigations of: **Microcytic hypochromic anemia**.
3. Investigations specific for: **THALASSEMIA:**
   - o Hb electrophoresis: ↑↑ Hb F (> 80 – 90 %): ***the most important investigation.***
   - o X- ray : **Skull** (hair-on-end appearance), **Long bones** (thin cortex & wide medulla).
   - o Serum Iron: ↑↑ iron, ↑↑ ferritin, ↑↑ transferrin iron saturation, ↓↓ TIBC.
   - o Blood film: characteristic **Target cells**.

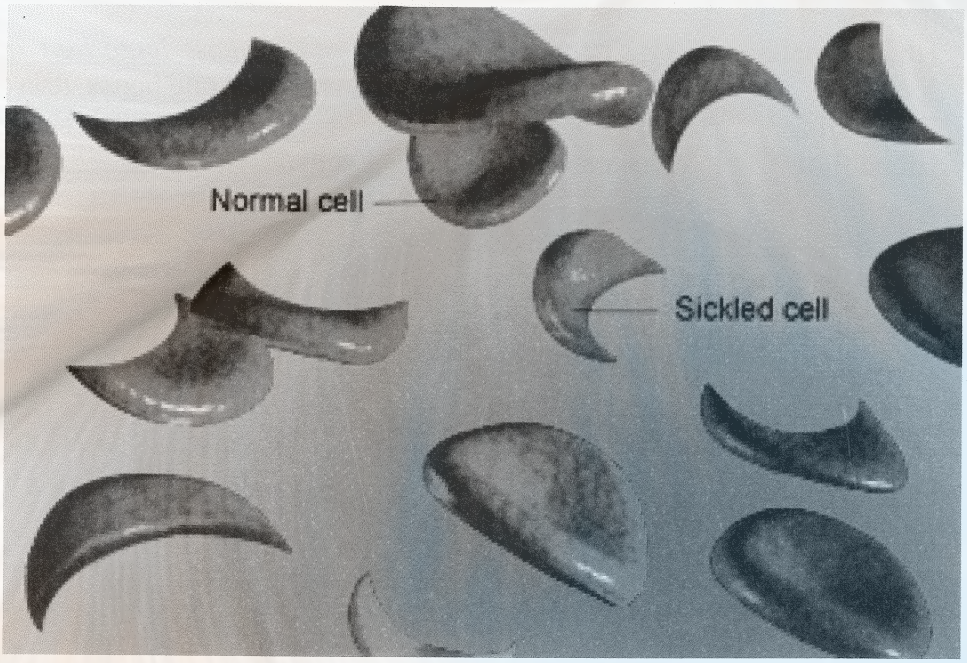
TREATMENT

1. **Specific ttt:**
   a. *Repeated packed red cell transfusion:* *to keep Hb > 10 gm %.*
   b. *Iron chelation:* *desferrioxamine by SC infusion.*
   c. *Folic acid:* *1 mg / day.*
   d. *Splenectomy:* *in case of hypersplenism.*
2. **New lines of ttt:** BMT, Gene therapy, Hydroxyurea.
3. **Prevention:** Prenatal diagnosis.

Beta – thalassemia with microcytes & target cells



Sickle cells



SICKLE CELL ANEMIA

ETIOLOGY

- A hereditary disorder in which there is production of an abnormal hemoglobin: **Hb S**.
- It may be ***homozygous*** (sickle cell anemia), or ***heterozygous*** (sickle cell trait).
- On exposure to ***HYPOXIA***, ***Infection***, or ***Acidosis***, Hb S will form insoluble aggregates:
  - RBCs become sickle-shaped → appear on blood film.
  - RBCs become less deformable → destruction **(Hemolysis)**.
  - RBCs show impaired flow → vascular **Occlusion** & tissue infarction.

CLINICAL PICTURE

- Incidence: it is common in black persons of African origin.

1. HEMOLYTIC ANEMIA.

2. VASO-OCCLUSIVE CRISES:

- **Bone** infarction: **" The most common occlusion "**
  - Painful crisis: attacks of severe pain in the ***back***, ***chest***, or ***extremities*** ± low grade fever.
  - Avascular necrosis: of the head of the femur.

• Cerebral occlusion:	hemiplegia	&	fits.
• Pulmonary occlusion:	acute pulmonary infarction,	or	corpulmonale.
• Hepatic occlusion:	abnormal biochemistry	&	pain.
• **SPLENIC** infarction:	autosplenectomy	&	hyposplenism.
• Renal infarction:	hematuria	&	renal failure.
• Retinal infarction:	retinal detachment	&	blindness.
• Penile occlusion:	priapism	or	impotence.

3. OTHER CLINICALL MANIFESTATIONS:

- Increased susceptibility to **INFECTIONS**: " Due to hyposplenism "
  - Pneumococcal infections.
  - Osteomyelitis caused by: *Staph. aureus* & *Salmonella*.

INVESTIGATIONS

1. General investigations of: **Hemolytic anemia**.
2. Investigations specific for: **SICKLE CELL ANEMIA:**
   - Hb electrophoresis: detects the abnormal " **Hb S** " ***the most important investigation.***
   - Blood film: characteristic **Sickle cells** esp. after inducing hypoxia by adding Na bisulphate.

TREATMENT

1. **Specific ttt:**
   a. *Repeated packed red cell transfusion:* *to keep Hb > 10 gm %.*
   b. *Iron chelation:* *desferrioxamine by SC infusion.*
   c. *Folic acid:* *1 mg / day.*
   d. *Symptomatic ttt:* *analgesics for painful crisis.*
2. **New lines of ttt:** BMT, Gene therapy, Hydroxyurea.
3. **Prevention:** Prenatal diagnosis.

G6PD DEFICIENCY

PATHOGENESIS

- ***Normally:***
  - RBCs are protected from **oxidizing stress** by the **HMP** through producing reduced glutathione.
  - RBCs contain G6PD enzyme which is essential for the **HMP**.

- ***In G6PD deficiency:***
  - RBCs do not contain G6PD & therefore will be unable to tolerate **oxidizing stress.**
  - **INTRAVASCULAR** hemolysis of the RBCs will occur.

CLINICAL PICTURE

- Incidence: It is an X-linked disease affecting mainly males.
- The patient develops **acute intravascular hemolysis** when subjected to **oxidizing stress:**

ACUTE INTRAVASCULAR HEMOLYSIS

- Anemia.
- Hemolytic jaundice.
- Hemoglobinuria.

OXIDIZING STRESSES

- **I**atrogenic: **A**spirin, **A**ntimalarials, **A**ntibacterials (e.g. sulphonamides).
- **I**nfections: Pyogenic infections & viral hepatitis.
- **M**etabolic: DKA & CRF.
- **M**eals: Ingestion of Fava bean (FAVISM).

- FAVISM:
  - ***Incidence:*** It is present almost only in Mediterranean populations.
  - ***Clinical picture:*** It presents by acute hemolysis after ingestion of fava beans.
  - ***Pathogenesis:*** It is not well understood, BUT it may be due to abnormal metabolism of beans resulting in production of oxidizing agents.

INVESTIGATIONS

1. General investigations of: **Hemolytic anemia**.
2. Investigations of: **INTRAVASCULAR** HEMOLYSIS.
3. Investigations specific for: **G6PD deficiency:**
   - *Estimation of G6PD.*

TREATMENT

1. Avoid oxidative stress: e.g. *responsible drugs*.
2. Repeated packed red cell transfusion: *in severe cases*.

AUTOIMMUNE HEMOLYTIC ANEMIA

A. Due to warm-reacting antibodies: *"most active at 37° C"*

ETIOLOGY

1. Idiopathic.
2. Secondary: *SLE, CLL, Lymphoma.*
3. Iatrogenic: *Drugs (see later).*

CLINICAL PICTURE

1. GENERAL MANIFESTATIONS OF: *HEMOLYTIC ANEMIA.*
2. SPECIFIC MANIFESTATIONS OF: the cause in secondary cases e.g. *SLE.*

INVESTIGATIONS

1. General investigations of: **Hemolytic anemia**.
2. Investigations specific for: **AIHA:** *Positive Coomb's test.*
3. Investigations for diagnosis of: the cause in secondary cases e.g. *SLE.*

TREATMENT

1. CORTICOSTEROIDS: *Prednisone* **1 mg / Kg / day orally.**
2. Immunosuppressive drugs: e.g. *cyclophosphamide.*
3. Transfusion therapy: may be needed in severe cases.
4. Splenectomy: may be needed in severe cases.

B. Due to cold-reacting antibodies: *"most active at 4° C"*

I. COLD AGGLUTININ DISEASE

- Presence of antibodies (**IgM**) that cause **Agglutination** of RBCs on exposure to cold.

ETIOLOGY

1. Idiopathic.
2. Secondary: *IMN* & *Mycoplasma pneumonia*.

CLINICAL PICTURE

1. Hemolytic anemia: *on exposure to cold.*
2. Raynaud's phenomenon: *on exposure to cold.*

INVESTIGATIONS

1. General investigations of: **Hemolytic anemia**.
2. Investigations specific for: **AIHA:** *Positive Coomb's test.*
3. Investigations for diagnosis of: the cause, *e.g.* *Mycoplasma pneumonia*.

TREATMENT

1. CORTICOSTEROIDS: of little benefit.
2. Immunosuppressive drugs: e.g. *cyclophosphamide*.
3. Transfusion therapy: may be needed in severe cases.
4. Splenectomy: of little benefit.
5. Avoid exposure to cold.

II. PAROXYSMAL COLD HEMOGLOBINURIA

- Presence of antibodies (**IgG**) that cause **Hemolysis** of RBCs on exposure to cold.

ETIOLOGY

1. Idiopathic.
2. Secondary: *Syphilis* & *Viral infections*.

CLINICAL PICTURE

- Hemolytic anemia: on exposure to cold.

INVESTIGATIONS

1. General investigations of: **Hemolytic anemia**.
2. Investigations specific for: **AIHA:** *Positive Coomb's test.*
3. Investigations for diagnosis of: the cause, *e.g.* *Syphilis*.

TREATMENT

- Same as: Cold agglutinin disease.

COOMB'S TEST

- It is the test used for diagnosis of autoimmune hemolytic anemia.

- It is of 2 types:

  - Direct Coomb's test:
    - *Aim:* To detect antibodies **coating** the RBCs.
    - *Method:* The patient's RBCs are mixed with Coomb's serum.
    - *Result:* Agglutination indicates a positive direct test.
  - Indirect Coomb's test:
    - *Aim:* To detect antibodies circulating **freely** in the serum.
    - *Method:* The patient's serum is incubated with compatible RBCs. These RBCs are then washed & mixed with Coomb's serum.
    - *Result:* Agglutination indicates a positive indirect test.

DRUG INDUCED HEMOLYSIS

- **Drugs may induce hemolysis through several mechanisms:**

1. **Direct damage:** of the membrane of the RBCs.
   - e.g. Amphotericin B.
2. **Oxidant drugs:** in patients with G6PD deficiency.
   - e.g. **A**spirin, **A**ntimalarials, **A**ntibacterials (e.g. sulphonamides).
3. **IMMUNE MECHANISMS:**
   - Autoimmune reaction:
     - The drug induces the production of an antibody which destroys the RBCs.
     - e.g. *alpha-methyl dopa*.
   - Hapten-like reaction:
     - The drug binds to the membrane of the RBC acting as a hapten.
     - e.g. *penicillin*.
   - Innocent bystander reaction:
     - The drug binds to its antibody on the surface of the RBC → complement activation.
     - e.g. *chlorpropamide* & *sulphonamides*.

APLASTIC ANEMIA

DEFINITION

- A disease characterized by: *hypocellular bone marrow* & *peripheral blood pancytopenia*.
- Aplastic anemia: anemia due to **Bone marrow failure**.

ETIOLOGY

I. APLASTIC ANEMIA "Pancytopenia"

a. Hereditary: Fanconi's anemia.

b. Acquired:

1. **I**diopathic: The most common cause (about 50 % of the cases).
2. **I**atrogenic: Dose-dependent OR Non Dose-dependent (idiosyncratic)
   - *Antibiotics:* e.g. ***CHLORAMPHENICOL.***
   - *Anti-inflammatory:* e.g. *NSAIDs & Gold.*
   - *Antiepileptics:* e.g. *phenytoin.*
   - *Antithyroid:* e.g. *carbimazole.*
   - *Antidiabetics:* e.g. *chlorpropamide.*
   - *Antineoplastics:* e.g. *chlorambucil.*
3. **I**nfections: **PARVOVIRUS B19, HBV, HCV**, HIV, EBV.
4. **I**nsecticides: and chemicals as **BENZENE**.
5. **I**mmune: SLE (rare).
6. **I**rradiation.
7. OTHERS: PNH, Pregnancy.

II. UNICELLULAR APLASTIA "Monocytopenia"

a. Pure red cell aplasia: e.g. *associated with Thymoma, aplastic crisis of HA.*

b. Granulocytopenia: e.g. *Cyclic neutropenia.*

c. Thrombocytopenia: e.g. *TAR syndrome* (**T**hrombocytopenia, **A**bsent **R**adius, *ASD*).

CLINICAL PICTURE

- **ANEMIA** (due to ↓ RBCs).
- **INFECTIONS** (due to ↓ WBCs).
- **BLEEDING** (due to ↓ Platelets).

} **PANCYTOPENIA**

INVESTIGATIONS

1. **CBC:** *" Pancytopenia "*
   - RBCs: NN anemia: with ***reticulocytopenia***.
   - WBCs: Leukopenia.
   - PLATELETS: Thrombocytopenia.

2. **Bone marrow examination:** *" Aspiration & biopsy "*
   - Hypocellular fatty BM devoid of hematopoietic precursor cells.

3. **Investigations for the cause:** *e.g. markers for HBV & HCV.*

DIFFERENTIAL DIAGNOSIS

1. Other causes of: PANCYTOPENIA.
2. Acute leukemia.

TREATMENT

I. Supportive TTT:

1. For anemia: packed RBCs transfusion.
2. For infections: antibiotics, G-CSF.
3. For bleeding: platelet transfusion.

II. Specific TTT:

- Withdrawal of the offending drug & ttt of the cause, ***plus:***

1. BMT: It is the only curative ttt & is indicated in
   - **P**rogressive: severe aplastic anemia.
   - **P**atients less than: **45** years.
   - **P**resence of: a suitable donor.

2. Immunosuppressive therapy: " Undefined mechanisms "
   - **C**yclosporin.
   - **C**orticosteroids: High dose.
   - Antithymocyte globulin (ATG).

3. Bone marrow stimulants:
   - Androgens.

CAUSES OF PANCYTOPENIA

1. **B**one marrow failure: *Aplastic anemia.*
2. **B**one marrow infiltration. *Myelophthisic anemia.*
3. Megaloblastic anemia.
4. Myelodysplastic syndromes.
5. PNH.
6. SLE.
7. Overwhelming infections.
8. Disseminated TB.
9. Hypersplenism.

CAUSES OF BM INFILTRATION

" **BM biopsy is the diagnostic procedure** "

1. **M**yelofibrosis:
   - Idiopathic.
2. **M**alignancy:
   - Blood malignancies: *Leukemias, Lymphomas.*
   - Solid malignancies: *BM metastases.*
3. **M**etabolic:
   - Lipid storage diseases: *Gaucher's disease.*
4. **M**assive infections:
   - TB *(miliary).*
   - Fungi.

CHLORAMPHENICOL & BM SUPPRESSION

1. Dose-related suppression:
   - Transient reversible aplastic anemia.
2. Non Dose-related suppression: " *Idiosyncrasy* "
   - Severe fatal irreversible aplastic anemia.

MEGALOBLASTIC ANEMIA

DEFINITION

- **Anemia in which there is impaired DNA synthesis due to deficiency of Vitamin B_{12} or / and folic acid:**
  - Delayed division of the rapidly proliferating cells (Hematopoietic cells, GIT, Skin).
  - Production of MEGALOBLASTS in the BM & MACROCYTES in the peripheral blood.

ETIOLOGY

I. VITAMIN B_{12} DEFICIENCY

1. Decreased intake:

- Lack of animal products.
- Vegetarian individuals.

2. Decreased absorption:

a) Deficient intrinsic factor: ***pernicious anemia, gastrectomy, atrophic gastritis.***
b) General Malabsorption syndrome: ***general causes of malabsorption including bacterial overgrowth.***
c) Specific Vitamin B_{12} malabsorption: ***Diphyllobothrium latum infestation or ileal affection.***

3. Increased demand:

- Infancy.
- Pregnancy.
- Malignancy.
- Chronic hemolysis.

II. FOLIC ACID DEFICIENCY

1. Decreased intake:

- Lack of vegetables.
- Excessive alcohol intake.

2. Decreased absorption:

- General Malabsorption syndrome: ***general causes of malabsorption.***
- Specific folic acid malabsorption: ***Drugs: anticonvulsants, CCPs.***

3. **Increased demand:**
   - Infancy.
   - Pregnancy.
   - Malignancy.
   - Chronic hemolysis.

4. **Folic acid antagonists:**
   - Methotrexate.
   - Co-trimoxazole.

PERNICIOUS ANEMIA

Atropy of the gastric mucosa → **decreased secretion of intrinsic factor (IF) & B_{12} deficiency**.
It is probably due to: **autoimmune** disease which may be **genetically** determined leading to:

- *Antiparietal cell antibodies that block the production of IF.*
- *Anti-IF antibodies that block the function of IF.*

It may be associated with other autoimmune diseases:
- *Autoimmune thyroiditis.*
- *Addison's disease.*

PATHOPHYSIOLOGY

- **Vitamin B_{12} & folic acid deficiency:** Both are essential for DNA synthesis, so their deficiency will lead to deficient DNA synthesis in the dividing cells → ***Delayed division.***

- **In the Bone Marrow:** Delayed division will result in the production of MEGALOBLASTS instead of the Normoblasts. Since these Megaloblasts are abnormal cells, they will be destroyed in the bone marrow ***(Intramedullary hemolysis).***

- **In the peripheral blood:** Megaloblasts that are formed in the bone marrow will lose their nuclei and reach the peripheral blood as MACROCYTES which are large cells with increased MCV. Many of these Macrocytes are taken by the spleen and destroyed ***(Extramedullary hemolysis).***

- **ANEMIA** will result due to:
  - Delayed division of erythroid precursors.
  - Excessive hemolysis (Intramedullary & Extramedullary).

- **LEUKOPENIA & THROMBOCYTOPENIA:** similarly occur due to deficient DNA synthesis.

- **PANCYTOPENIA:** will finally occur.

- **OTHERS:**

  GIT: Cells in the GIT show the same defect, leading to secondary atrophy of the epithelial cells of the: ***tongue, stomach, small intestine.***

  CNS: Inability to synthesize myelin is present ***ONLY*** in B_{12} deficiency and leads to neurological manifestations (Absent in folic acid deficiency).

CLINICAL PICTURE

1. HEMATOLOGICAL MANIFESTATIONS

- **ANEMIA** (due to ↓ RBCs).
- **INFECTIONS** (due to ↓ WBCs).
- **BLEEDING** (due to ↓ Platelets).

} **PANCYTOPENIA**

- HEPATOSPLENOMEGALY.

2. GIT MANIFESTATIONS

- Tongue: ***Atrophic*** glossitis (glazed tongue).
- Stomach: ***Atrophic*** gastritis (dyspepsia, anorexia, nausea, vomiting).
- Intestine: Intestinal ***Atrophy*** (abdominal pain, diarrhoea, malabsorption).

3. NEUROLOGICAL MANIFESTATIONS *"Only In B_{12} Deficiency"*

- Peripheral neuropathy.
- SCD of the spinal cord (refer to neurology).

4. ASSOCIATED AUTOIMMUNE DISEASES *"Only In Pernicious anemia"*

- Autoimmune thyroiditis.
- Addison's disease.

INVESTIGATIONS

1. CBC:

a) RBCs:

- Features of macrocytic anemia:
  - Decreased: Red cell count, Hemoglobin level, Hematocrit value.
  - Increased: MCV **(LARGE RBCs).**
- Reticulocytosis: after giving ttt (anemia under ttt).

b) WBCs:

- Leukopenia: → with shift to the right.
- **LARGE NEUTROPHILS** (Hypersegmented).

c) Platelets:

- Thrombocytopenia.
- **LARGE PLATELETS.**

2. Bone marrow examination:

- Hypercellular megaloblastic bone marrow.
- Giant cells with abnormal morphology.

3. Blood chemistry:

- Increased: serum indirect bilirubin.
- Increased: serum iron.
- Increased: serum LDH.

4. Serum B12 & serum folic acid: *" done by radio-immunoassay "*

- Decreased.

5. Schilling test: *" Only In B_{12} Deficiency "*

- Unlabelled B_{12} is given: (1000 ug IV) to saturate the body stores.
- Radiolabelled B_{12} is then given: (1 ug orally).
- The patient's urine is collected for 48 hours: measure exreted Radiolabelled B_{12}.
- If excretion is low: **B_{12} malabsorption is diagnosed:**
  - In *pernicious anemia*: **excretion becomes normal after giving IF orally.**
  - In *bacterial overgrowth*: **excretion becomes normal after giving Antibiotics.**
  - In *pancreatic insufficiency*: **excretion becomes normal after giving Pancreatic enzymes.**

6. Serology: "*Only In Pernicious anemia*"

- Antiparietal cell antibodies.
- Anti-IF antibodies.

7. FIGLU test: "*Only In Folic Deficiency*"

- *Normally*:

  Orally given HISTIDINE is transformed into FIGLU which is converted in the presence of folic acid into glutamic acid which is excreted in urine.

- *In foilc acid deficiency*:

  Oral administration of HISTIDINE will lead to excessive excretion of FIGLU in urine (instead of glutamic acid).

8. Therapeutic tests:

- Giving small doses of Vitamin B12 or Folic acid → Reticulocytosis.

TREATMENT

1. Replacement therapy:

a) In B12 deficiency:

- Hydroxycobalamin or cyanocobalamin: 500 – 1000 ug IM / day for 2 weeks.
- Then: once / week until anemia is corrected.
- Then: once / month for life.

b) In folic acid deficiency:

- Folic acid: 1-5 mg / day orally.
- Parentral administration may be needed: e.g. in malabsorption.
- Therapy for: 1 month is sufficient to correct the anemia.
- B12 deficiency should be excluded before giving folic acid since it may aggravate: *the neurological manifestations*.

2. Transfusion therapy:

- Packed red cell transfusion may be needed in cases of severe anemia:
  - Hemoglobin: < 7 gm %.
  - Marked symptoms of anemia.
  - Anemic HF.

3. TTT of the cause & symptomatic ttt of anemia.

OTHER ANEMIAS

1. ANEMIA OF CHRONIC DISEASE (ACD).
2. ANEMIA OF LIVER DISEASE.
3. ANEMIA OF UREMIA.
4. SIDEROBLASTIC ANEMIA.
5. ANEMIA OF ENDOCRINE DISORDERS.
6. ANEMIA OF PREGNANCY.
7. ACUTE POST- HEMORRHAGIC ANEMIA.

ANEMIA OF CHRONIC DISEASE (ACD)

DEFINITION

- It is a type of anemia seen in chronic illness.
- Incidence: it is the ***2nd most common*** type of anemia.
- Severity: it is usually ***mild to moderate***.

ETIOLOGY

1. Chronic infection (e.g. TB).
2. Chronic inflammation (e.g. RA, SLE, IBD).
3. Malignancy (Blood, Solid).

PATHOGENESIS

1. Reduced life span of RBCs.
2. Impaired release of iron.
3. Erythropoietin (EPO) defect:
   - ↓ *production of EPO.*
   - ↓ *response to EPO in the BM.*

CLINICAL PICTURE

1. Clinical picture of the cause.
2. General clinical picture of anemia (*usually mild*).

INVESTIGATIONS

1. Investigations of the cause.
2. **Microcytic hypochromic** anemia **or**: NN anemia.
3. Serum iron: decreased, Serum ferritin: normal or increased.

DIFFERENTIAL DIAGNOSIS

- Causes of: Microcytic anemia:

1. Iron deficiency anemia.
2. *Thalassemia.*
3. *Sideroblastic anemia.*
4. *Anemia of chronic disease* *(ACD).*

TREATMENT

1. TTT of the cause.
2. Recombinant EPO.

ANEMIA OF LIVER DISEASE

1. Liver cell failure: Refer to " Liver notes ".
2. Hepatitis: Aplastic anemia with HBV, HCV.
3. Wilson's disease: Hemolytic anemia.
4. HCC: ACD.
5. Lipid storage disease: Myelophthisic anemia (BM infiltration).

ANEMIA OF UREMIA

- Incidence: Common.
- Severity: Usually related to the degree of uremia.
- PATHOGENESIS:

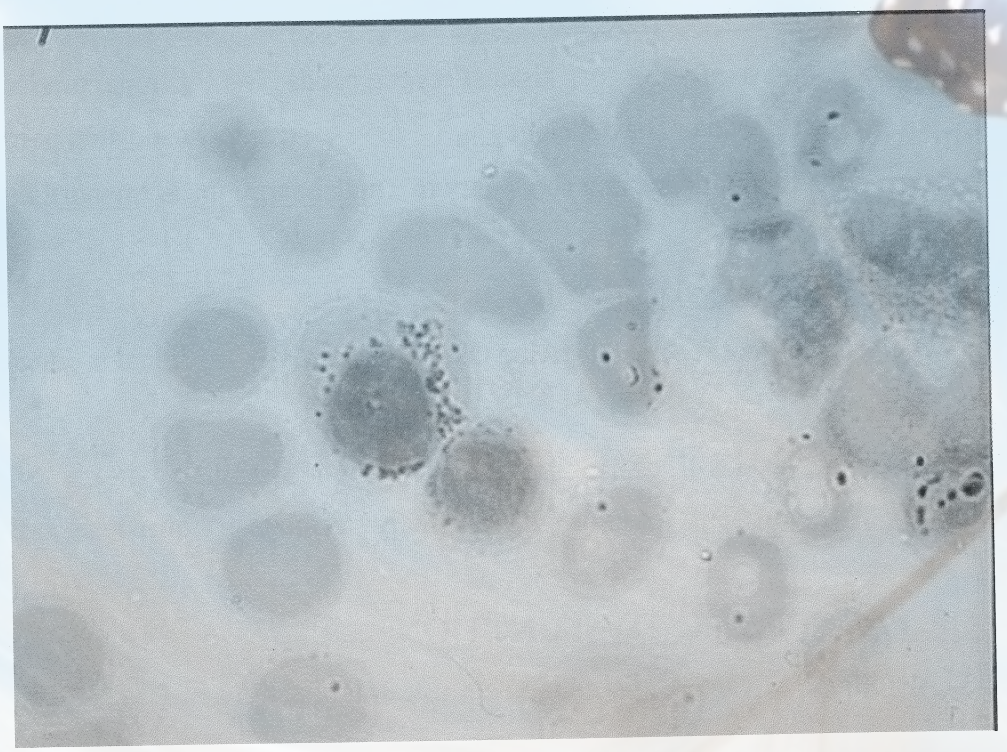
  - ↓ **production of EPO.**
  - ↓ iron.
  - ↓ vitamins (folic acid, vitamin B_{12}).
  - ↓ life span of RBCs (hemolysis).
  - HYPERPARATHYROIDISM.

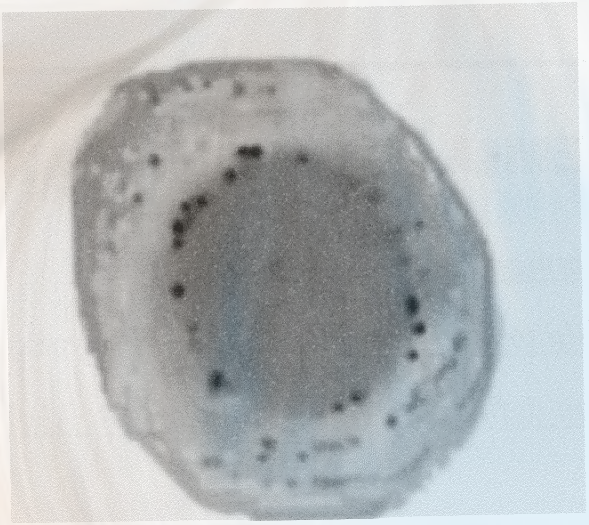
- CP: CP of uremia + general CP of anemia.
- Investigations: NN anemia + SCHISTOCYTES + impaired renal functions.
- Treatment: TTT of uremia, recombinant EPO.

SIDEROBLASTIC ANEMIA

- Etiology:
  - Hereditary.
  - Acquired: (***Idiopathic:*** MDS or ***Secondary:*** RA, Malignancy, Lead).
- Pathogenesis: Inability to use iron in the formation of Hemoglobin.
- Type: Microcytic hypochromic anemia.
- Diagnosis:
  - **Ringed sideroblasts** in BM: *Erythroblasts with a ring of iron granules around the nucleus.*
  - **Serum iron**: increased, **Serum ferritin**: increased.
  - **FEP**: increased.

Ringed sideroblasts





ANEMIA OF ENDOCRINE DISORDERS

1. ANEMIA OF HYPOPITUITARISM:
   - Normocytic: ↓ GH → ↓ tissue Oxygen needs → ↓ renal production of EPO.

2. ANEMIA OF HYPOTHYROIDISM:
   - Normocytic: ↓ Thyroxin → ↓ tissue Oxygen needs → ↓ renal production of EPO.
   - Macrocytic: **due to folic or B_{12} deficiency or due to associated pernicious anemia.**
   - Microcytic: **due to iron deficiency secondary to malabsorption & menorrhagia in females.**

3. ANEMIA OF ADDISON'S DISEASE:
   - Normocytic: ↓ Cortisol → ↓ tissue Oxygen needs → ↓ renal production of EPO.

4. ANEMIA OF GONADAL DYSFUNCTION: **[In males]**
   - Normocytic: ↓ Androgens (Androgens normally stimulate erythropoesis in BM).

5. ANEMIA OF PANCREATIC DYSFUNCTION:
   - Anemia is common in DM: due to chronic complications of DM, e.g. CRF.

6. ANEMIA OF PARATHYROID DYSFUNCTION:
   - Anemia may occur in Hyperparathyroidism: due to ↓ EPO production & BM calcification.

ANEMIA OF PREGNANCY

- Incidence: ***common***.
- Severity: ***Mild to moderate***, (about the 8^{th} week of pregnancy).
- Etiology: ***iron deficiency***, ***folic or B_{12} deficiency***.

ACUTE POST- HEMORRHAGIC ANEMIA

ETIOLOGY

"Acute severe bleeding"

1. Trauma.
2. Surgery.
3. GIT ulcers.
4. Hemorrhagic blood diseases: **e.g.** *Hemophilia*, *Purpura*.

CLINICAL PICTURE

1. Evidence of: *BLEEDING*.
   (Bleeding from multiple sites suggests: Hemorrhagic blood diseases).
2. General clinical picture of anemia, *manifestations depend on:*
   - ***Rate*** *of bleeding.*
   - ***Amount*** *of bleeding.*
   - ***Time*** *between bleeding & presentaion.*
3. There are 2 chronological CLINICAL STAGES:
   A) FIRST STAGE: (lasts 1 – 3 days)
      - Manifestations of *hypovolemia.*

   B) SECOND STAGE: (after 1 – 3 days)
      - Manifestations of *hypovolemia* **disappear**.
      - Manifestations of *anemia.*

INVESTIGATIONS

1. Investigations of the cause.
2. CBC:
   - RBCs: anemia *(normocytic or macrocytic)*, reticulocytosis.
   - WBCs: leukocytosis.
   - PLATELETS: thrombocytosis *(reactive)*.

TREATMENT

1. Treatment of the cause.
2. Symptomatic treatment: **e.g.**
   - Correction of *hypovolemia,* e.g. Blood transfusion.
   - *For anemia.*

LEUKEMIAS

DEFINITION

- Neoplasms that arise from **malignant transformation** of hematopoietic or lymphoid cells.
- Leukemic cells (abnormal Leukocytes) proliferate primarily in the **BM**, & then circulate in the **peripheral blood** and infiltrate **other tissues**.

ETIOLOGY

- The cause is UNKNOWN.
- Predisposing factors include:
  - *Genetic:* Incidence in **identical twins** & in **chromosomal disorders**, e.g. Down's syndrome.
  - *Environmental* Irradiation, Chemicals as Benzene.
  - *Viral infection:* Retroviruses.
  - *Pre-existing disorders:* PNH, MDS.

CLASSIFICATION

1. **According to the clinical course:**
   - Acute leukemia: characterized by proliferation of IMMATURE CELLS = **BLASTS**.
   - Chronic leukemia: characterized by proliferation of MATURE CELLS = **CYTES**.
2. **According to the cell type:**
   - Lymphatic leukemia.
   - Myeloid leukemia.

INCIDENCE

- Acute & chronic leukemia are nearly of equal incidence.
- Age: leukemia may affect any age, HOWEVER:
  - ALL: more common in children & young adults.
  - AML: more common in adults.
  - CLL: more common in old age.
  - CML: more common in middle & old age.

ACUTE LEUKEMIA

INCIDENCE

- ALL: more common in children & young adults.
- AML: more common in adults.

CLINICAL PICTURE

A) MANIFESTATIONS OF BM FAILURE

1. **Anemia:** " **RBCs** "
   - Cause: encroachment on the Red cell precursors in the BM, or due to bleeding.
   - Description: *rapidly developing, progressive, severe.*
2. **Bleeding:** " **Platelets** "
   - Cause: encroachment on the Platelet precursors in the BM → **Thrombocytopenia**.
   - Description: *thrombocytopenic bleeding:* " see later ".
3. **Fever & recurrent infections:** " **WBCs** "
   - Cause: non-functioning abnormal WBCs.
   - Description: *in the form of:*
     i. Common sites of infection: **mouth, throat, anorectal region, UTI, lungs, skin**.
     ii. Common organisms:
     - *Gm + ve cocci:* *Staph. aureus.*
     - *Gm – ve bacilli:* *Pseudomonas.*
     - *Fungi:* *Candida.*
     - *Viruses:* *HSV.*

B) MANIFESTATIONS OF ORGAN INFILTRATION

1. **Lymphadenopathy:**
   - Generalized LN: of small or moderate size, especially in ALL.
   - Cervical LN: may be markedly enlarged & tender due to oral infection.
   - Pressure manifestations: e.g. *mediastinal syndrome* or *obstructive Jaundice*.
2. **Hepatosplenomegaly.**
3. **Generalized bone pains & STERNAL TENDERNESS.**

4. Leukostasis:

- Occlusion of the microcirculation leading to **Ischemia** in different tissues.
- It affects different tissues, MAINLY: *ears*, *eyes*, *brain*, *lungs*, *penis*.

5. Other organs affection:

CNS

- Brain: cranial nerve palsies.
- Spinal cord: focal paraplegia.
- Meninges: meningeal irritation.

LUNGS

- Hemoptysis.

KIDNEYS

- Hematuria, ARF.

BONES

- Bony pains & pathological fractures.

JOINTS

- Joint effusion & arthritis.

GIT

- Ulcers & hemorrhage.

GUMS

- Ulcers & hypertrophy, especially in: Monoblastic leukemia.

SKIN

- Rash & nodules.

SEROUS MEMBRANES

- Pericardial effusion, pleural effusion, ascites.

TESTIS

- Testicular swelling, especially in: ALL.

C) METABOLIC MANIFESTATIONS

- Hyperuricemia: may lead to urate nephropathy & gouty arthritis.
- Hypokalemia: may occur due to renal tubular defect.
- Hyponatremia: may occur due to " SIADH ".

INVESTIGATIONS

1. CBC:

- **WBCs:** "**Leukocytosis**"

1. TLC: Increased, may reach 100,000 / cmm.
2. Cells: BLASTS are predominant (*myeloblasts* or *lymphoblasts*).

3. SPECIFIC TYPES:
   i. Subleukemic leukemia: TLC is ***normal*** with presence of: **BLASTS.**
   ii. Aleukemic leukemia: TLC is ***normal*** with: **no BLASTS,**
   in this case the diagnosis depends on BM examination.

	Myeloblasts	Lymphoblasts
Cell morphology		
Cytochemistry	Myeloperoxidase + ve	PAS + ve

- **RBCs:**
  - Normocytic normochromic anemia.

- **PLATELETS:**
  - *Thrombocytosis*, **or** *Thrombocytopenia.*

2. Bone marrow examination:

- Hypercellular: infiltrated with sheets of BLASTS that replace the normal BM cells.
- BLASTS: more than 30 % & may reach up to 100 % of BM cells.
- BLASTS: *myeloblasts* or *lymphoblasts*.

3. Metabolic abnormalities:

- Serum uric acid: increased.
- Serum LDH: increased.
- Serum vitamin B_{12}: increased
- Serum potassium: *may be decreased.*
- Serum sodium: *may be decreased.*

DIFFERENTIAL DIAGNOSIS

1. CLINICALLY: *Acute leukemia should be differentiated from:*

- APLASTIC ANEMIA.
- *Fever with LN.*
- *Fever with sore throat.*
- Rheumatic fever.
- Miliary TB.

2. LEUKEMOID REACTION:

- It is defined as marked leukocytosis (25,000 / cmm) & may be associated with: IMMATURE LEUKOCYTES.

- Myeloid leukemoid reaction:
  - BM infiltration: (myelophthisic anemia).
  - BM stimulation: severe **H**emolysis, severe **H**emorrhage, severe **H**ypoxia.

- Lymphatic leukemoid reaction:
  - Hepatitis.
  - HSV, IMN, CMV.
  - TB, Brucellosis, Syphilis.

TREATMENT

I. Supportive ttt:

1. For anemia: packed red cell transfusion.
2. For bleeding: platelets transfusion.
3. For infections: isolation + *antibiotics, antifungal, antiviral drugs*.
4. For hyperuricemia: Allopurinol.
5. For leukostasis: Leukapheresis.

II. Specific ttt:

1. Chemotherapy with or without radiotherapy:

A) ALL:

1. Induction of remission: Vincristine, prednisone: *for 4 weeks*.
2. CNS prophylaxis: Intrathecal methotrexate.
3. Consolidation: Vincristine, prednisone.
4. Maintenance: Vincristine, prednisone , + methotrexate + 6 MP.

B) AML:

1. Induction of remission: Cytosine arabinoside, Daunorubicin: *for 7 days*.
2. Maintenance: Cytosine arabinoside, Daunorubicin: *for 1 year*.

2. BMT: It is indicated in:

- **P**rogressive: & refractory cases.
- **P**atients less than: 45 years.
- **P**resence of: a suitable donor.

CHRONIC MYELOID LEUKEMIA

MPD

CLINICAL PICTURE

A) MANIFESTATIONS OF ORGAN INFILTRATION

1. SPLENOMEGALY:

Pain:

- Dragging pain in the left hypochondrium: due to splenomegaly.
- Stitching pain in the left hypochondrium: due to perisplenitis, resulting from splenic infarction (due to *leukostasis* or *thrombosis*).

Spleen:

- HUGE size: usually occurs.
- SPLENIC RUB: is usually heard + multiple notches due to infarctions.

2. Hepatomegaly:

- The liver may also be enlarged, or even huge, with *rounded border*.

3. Lymphadenopathy:

- Slight LN enlargement occurs *rarely*.

4. Generalized bone pains & STERNAL TENDERNESS.

5. Leukostasis:

- Occlusion of the microcirculation leading to **Ischemia** in different tissues.
- It affects different tissues, MAINLY: *ears*, *eyes*, *brain*, *lungs*, *penis*.

6. Other organs affection:

- Leukemic infiltrations of other organs are RARE.

B) MANIFESTATIONS OF BM FAILURE

1. **Anemia.**
2. **Bleeding.**
3. **Fever & recurrent infections.**

C) METABOLIC MANIFESTATIONS

- Hyperuricemia: may lead to urate nephropathy & gouty arthritis.

D) BLAST CRISIS

- 70 % of the patients will eventually develop transformation into AML.

INVESTIGATIONS

1. CBC:

- **WBCs:** **" Leukocytosis "**
  1. TLC: Increased, may reach 100,000 - 1,000,000 / cmm.
  2. Cells: MYELOCYTES are predominant with few *MYELOBLASTS*.
     MYELOBLASTS increase markedly in Blast crisis.
  3. LAP: Decreased.

- **RBCs:**
  - Normocytic normochromic anemia.

- **PLATELETS:**
  - *Thrombocytosis*, **or** *Thrombocytopenia.*

2. Bone marrow examination:

- Hypercellular & full of MYELOCYTES, with few *MYELOBLASTS*.
- MYELOBLASTS increase markedly in Blast crisis.

BLAST CRISIS: 30 % or more MYELOBLASTS are present in the BM and / or peripheral blood.

3. Metabolic abnormalities:

- Serum uric acid: increased.
- Serum LDH: increased.
- Serum vitamin B12: increased.

4. The Philadelphia chromosome:

- Acquired chromosomal abnormality: present in 90 % of patients with CML.
- It results from: translocation of a part of the long arm of chromosome number 22 to the long arm of chromosome number 9.

DIFFERENTIAL DIAGNOSIS

1. CLINICALLY: *CML should be differentiated from:*

- CLL.
- Causes of: HUGE SPLENOMEGALY (see later).
- Causes of: Myeloproliferative disorders:
  - *CML.*
  - *PRV.*
  - *Essential thrombocythemia.*
  - *Idiopathic myelofibrosis.*

2. LABORATORY: LEUKEMOID REACTION: " see before "

- It is defined as marked leukocytosis (25,000 / cmm) & may be associated with: immature leukocytes.
- It is mainly differentiated from CML by:

	Leukomoid reaction	CML
Splenomegaly	Rare	Common
LAP	High	Low
Philadelphia chromosome	Absent	Present in 90 % of cases

TREATMENT

I. Supportive ttt:

1. For anemia: packed red cell transfusion.
2. For bleeding: platelets transfusion.
3. For infections: isolation + *antibiotics*, *antifungal*, *antiviral drugs*.
4. For hyperuricemia: Allopurinol.
5. For leukostasis: Leukapheresis.

II. Specific ttt:

1. Chemotherapy:

Busulfan: (Myeleran) 4 – 8 mg / day orally

- It should be stopped when TLC is reduced below 25,000 / cmm.
- Side effects: *BM failure, pulmonary fibrosis, vomiting & diarrhoea.*

Hydroxyurea: 1 – 6 **gm** / day orally

- It has less side effects & better results than Busulfan.

2. Interferon – alpha.

3. BMT:

It is the only curative ttt & is indicated in:

- **P**rogressive: & refractory cases.
- **P**atients less than: **30** years.
- **P**resence of: a suitable donor.

4. TTT of Blast crisis:

- TTT is similar to AML but with a *poor response*.

CHRONIC LYMPHATIC LEUKEMIA

- It is the most common form of leukemia in adults especially in: *old age*.
- CLL is closely related to (and most consider it the same as):
  SLL, small lymphocytic lymphoma a type of *non-Hodgkin's lymphoma*.

CLINICAL PICTURE

1. **Asymptomatic:** occurs in 25 % of the cases.

2. **LYMPHADENOPATHY:** " The most important manifestation "
   - Generalized LN: **of moderate size, firm, discrete, NOT TENDER.**
   - Pressure manifestations: **e.g. *mediastinal syndrome* or *obstructive Jaundice*.**

3. **Hepatosplenomegaly.**

4. **Leukemic infiltrations of other organs may occur.**

5. **Anemia:** *due to:*
   - Autoimmune hemolytic anemia (positive Coomb's test).
   - BM infiltration.
   - Hypersplenism.
   - Bleeding.

6. **Bleeding:** due to thrombocytopenia, *due to:*
   - Autoimmune thrombocytopenia.
   - BM infiltration.
   - Hypersplenism.

7. **Fever & recurrent infections.**

INVESTIGATIONS

1. CBC:

- **WBCs:** " Leukocytosis " MAINLY " Lymphocytosis "
  - TLC: Increased, may reach 100,000 - 1,000,000 / cmm.
  - Cells: SMALL LYMPHOCYTES are predominant.
- **RBCs:**
  - Normocytic normochromic anemia.
  - Hemolytic anemia: ***with positive Coomb's test.***
- **PLATELETS:**
  - *Thrombocytosis*, **or** *Thrombocytopenia.*

2. Bone marrow examination:

- Hypercellular & full of: SMALL LYMPHOCYTES (> 30 %).

3. Lymph node biopsy:

- Infiltration with: SMALL LYMPHOCYTES.

4. Metabolic abnormalities:

- Serum uric acid: increased.
- Serum LDH: increased.

DIFFERENTIAL DIAGNOSIS

- CML.
- Causes of: Lymphocytosis.
- Causes of: Generalized LN enlargement: *especially Lymphoma*.

TREATMENT

I. Supportive ttt:

1. For anemia: packed red cell transfusion.
2. For bleeding: platelets transfusion.
3. For infections: isolation + *antibiotics*, *antifungal*, *antiviral drugs*.
4. For hyperuricemia: Allopurinol.

II. Specific ttt:

1. Chemotherapy:

- Chlorambucil: (leukeran) 0.1 mg / Kg / day orally.
- Prednisone: 1 mg / Kg / day orally.

2. Radiotherapy:

- Irradiation of LN & spleen may be needed.

POLYCYTHEMIA

DEFINITION

- Increase in red cell mass: > 36 ml / Kg in males & > 32 ml / Kg in females.

ETIOLOGY

A) Secondary polycythemia:

1. **Chronic hypoxia** (e.g. COPD & other causes of chronic central cyanosis).
2. **Cushing's syndrome & prolonged corticosteroid therapy.**
3. **Renal disease** (e.g. hypernephroma & hydronephrosis) → ↑ EPO.
4. **Paramalignant syndrome** (e.g. HCC).
5. **Dehydration** → hemoconcentration (false polycythemia).

B) Polycythemia Rubra Vera: "PRV"

MPD

- A myeloproliferative disorder (blood malignancy) characterized by:

"Excessive proliferation of"

ERYTHROIDS in BM → ↑ *RBCs* ***in the peripheral blood.***
MYELOIDS in BM → ↑ *WBCs* *in the peripheral blood.*
MEGAKARYOCYTES in BM → ↑ *Platelets* *in the peripheral blood.*

CLINICAL PICTURE

1. Plethoric appearance.

2. Symptoms due to Hyperviscosity:

- Neurological: *headache, dizziness, tinnitus, blurring of vision, parasthesias.*
- CVS: *dyspnea, palpitation, precipitation of angina.*
- EYE: *conjunctival suffusion, retinal venous engorgement.*

3. In PRV:

- MANIFESTATIONS:
  - Hepatomegaly.
  - SPLENOMEGALY: HUGE size.
  - Peptic ulcer: due to associated increase in Histamine level.
  - Pruritus.
- COMPLICATIONS:
  - Vascular thrombosis: *e.g. Stroke.*
  - Bleeding tendency. *e.g. Stroke.*
  - ***Hyper***tension.
  - ***Hyper***uricemia.

4. In secondary polycythemia:

- Features of the cause.

INVESTIGATIONS

1. CBC:

- **RBCs:**
  - Increased number (above 6 million / cmm).
- **WBCs:**
  - Increased number (above 12,000 / cmm).
- **PLATELETS:**
  - Increased number (above 400,000 / cmm).

} In PRV ONLY

2. Bone marrow examination:

- HYPERCELLULARITY of ALL bone marrow elements. **In PRV ONLY**

3. ESR: Low.

4. Red cell mass:

- Increased: > 36 ml / Kg in males & > 32 ml / Kg in females.

5. Tests to differentiate between Secondary polycythemia & PRV:

A. ARTERIAL BLOOD GASES:

- In secondary polycythemia: Decreased oxygen saturation.
- In PRV: Normal oxygen saturation.

B. SERUM EPO:

- In secondary polycythemia: Increased.
- In PRV: Normal or low.

6. Others:

- Serum uric acid: increased.
- Serum LAP: increased.
- Serum vitamin B12: increased.

DIAGNOSIS OF PRV

A

A1: Increased Red cell mass: > 36 ml / Kg in ♂ & > 32 ml / Kg in ♀.
A2: Normal oxygen saturation.
A3: Splenomegaly.

B

B1: Increased Platelets: > 400,000 / cmm.
B2: Increased WBCs: > 12,000 / cmm.
B3: Increased LAP.
B4: Increased serum vitamin B12.

- DIAGNOSIS is established if the following combinations are present:
  - A1 + A2 + A3, or:
  - A1 + A2 + *any 2 from category B*.

TREATMENT

A) PRV

1. Repeated venesection: *to keep the Hematocrit value in the range of* **45 %**.
2. Chemotherapy:
   - Hydroxyurea: is the best.
   - Radioactive phosphorus, Busulphan: may be used.
3. TTT of complications.

B) Secondary polycythemia:

1. Repeated venesection: *to keep the Hematocrit value in the range of* **45 %**.
2. TTT of the cause.

IDIOPATHIC MYELOFIBROSIS

MPD

DEFINITION

- Progressive generalized fibrosis of the BM, associated with:
- Haemopoiesis in the ***liver*** & ***spleen*** (known as: Myeloid Metaplasia).

ETIOLOGY UNKNOWN

EARLY Idiopathic abnormal change in the ***stem cell*** in the BM leading to:

- Decreased production of: RBCs.
- Increased production of: WBCs.
- Increased production of: abnormal MEGAKARYOCYTES.
- Abnormal Megakaryocytes secrete: GROWTH FACTORS.
- Growth factors stimulate: FIBROBLASTS to produce fibrosis of BM.

LATE Excessive BM fibrosis will ↓↓ the ability of the BM to make blood cells:
→ Decreased all blood cells → PANCYTOPENIA.

CLINICAL PICTURE

1. Decreased RBCs: General manifestations of anemia.
2. Decreased WBCs: Fever & recurrent infections.
3. Decreased platelets: Purpura & bleeding tendency.

4. SPLENOMEGALY: HUGE size.
5. Hepatomegaly: Mild.

INVESTIGATIONS

1. **CBC:** *" Pancytopenia "*
   - RBCs: Normocytic normochromic anemia: with ***teardrop RBCs***.
   - WBCs: Early Leukocytosis, Late Leukopenia.
   - PLATELETS: Early Thrombocytosis, Late Thrombocytopenia.

2. **Bone marrow examination:** *" Aspiration & biopsy "*
   - Aspiration: BM specimen cannot be obtained.
   - Biopsy: Fibrotic BM.

DIFFERENTIAL DIAGNOSIS

1. Other causes of: PANCYTOPENIA.
2. Other causes of: HUGE SPLENOMEGALY.
3. Other causes of: Myeloproliferative disorders.

TREATMENT

I. Supportive TTT:

- For deficient blood cells: Repeated Blood transfusion.
- For splenomegaly: Splenectomy ***or*** radiotherapy (spleen shrinkage).

II. Specific TTT:

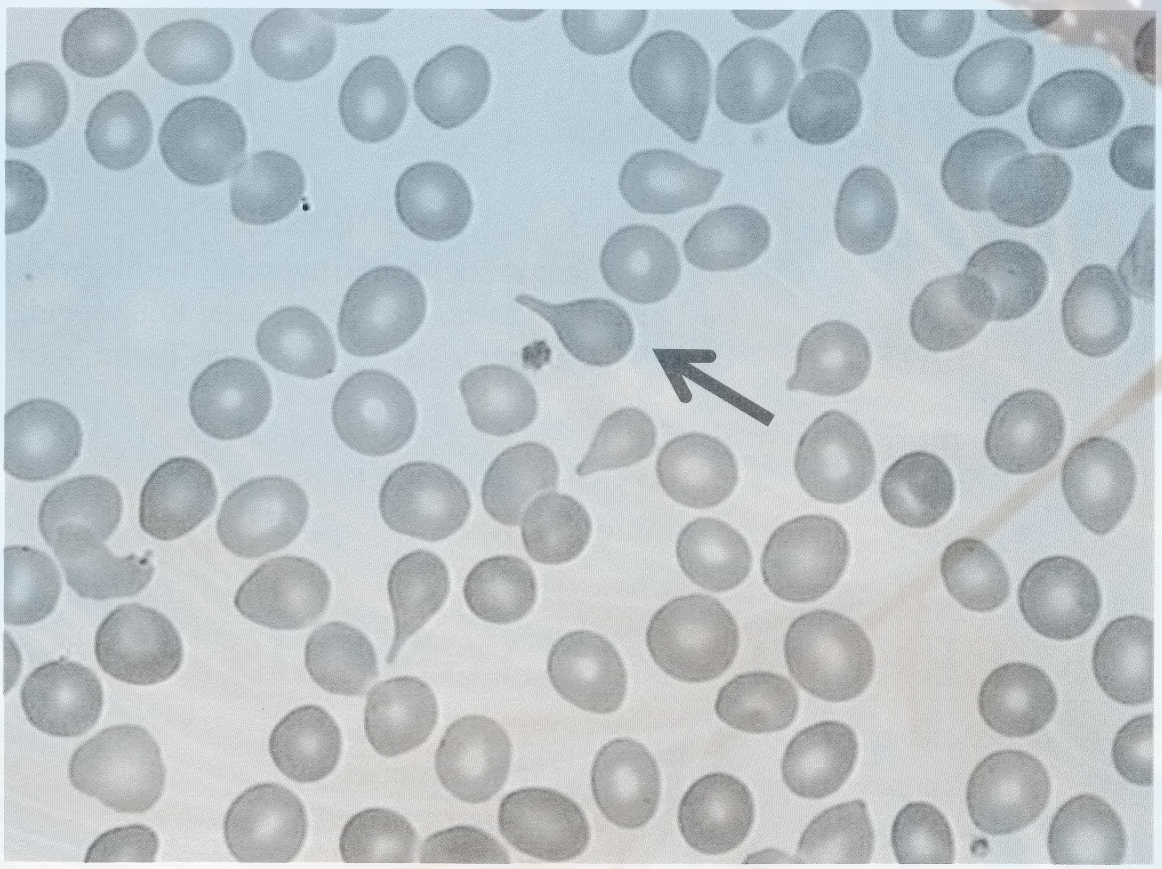
1. Chemotherapy:

- Hydroxyurea.

2. Stem cell transplantation:

- It is the only hope for cure.

Teardrop RBCs in Idiopathic myelofibrosis



NORMAL HEMOSTASIS

Three mechanisms are involved to prevent bleeding from injured blood vessels:

1. VESSEL WALL:

- Vasoconstriction of injured vessel is IMMEDIATE & involves **2 events**:
- Reflex vasoconstriction of adjacent arteries & arterioles: *this slows the blood flow to the area of injury.*
- Slow blood flow to the area of injury: *will allow contact activation of platelets & coagulation factors.*

2. PLATELET REACTION: " PRIMARY HEMOSTASIS "

- It occurs within SECONDS of injury & involves **3 events**:
- Platelet adhesion: *to the exposed subendothelium is the initial response.*
- Platelet aggregation: *then occurs to form the obstructing platelet plug.*
- Granule release: *accelerates coagulation process by providing Ph L. accelerates clot retraction / compaction.*

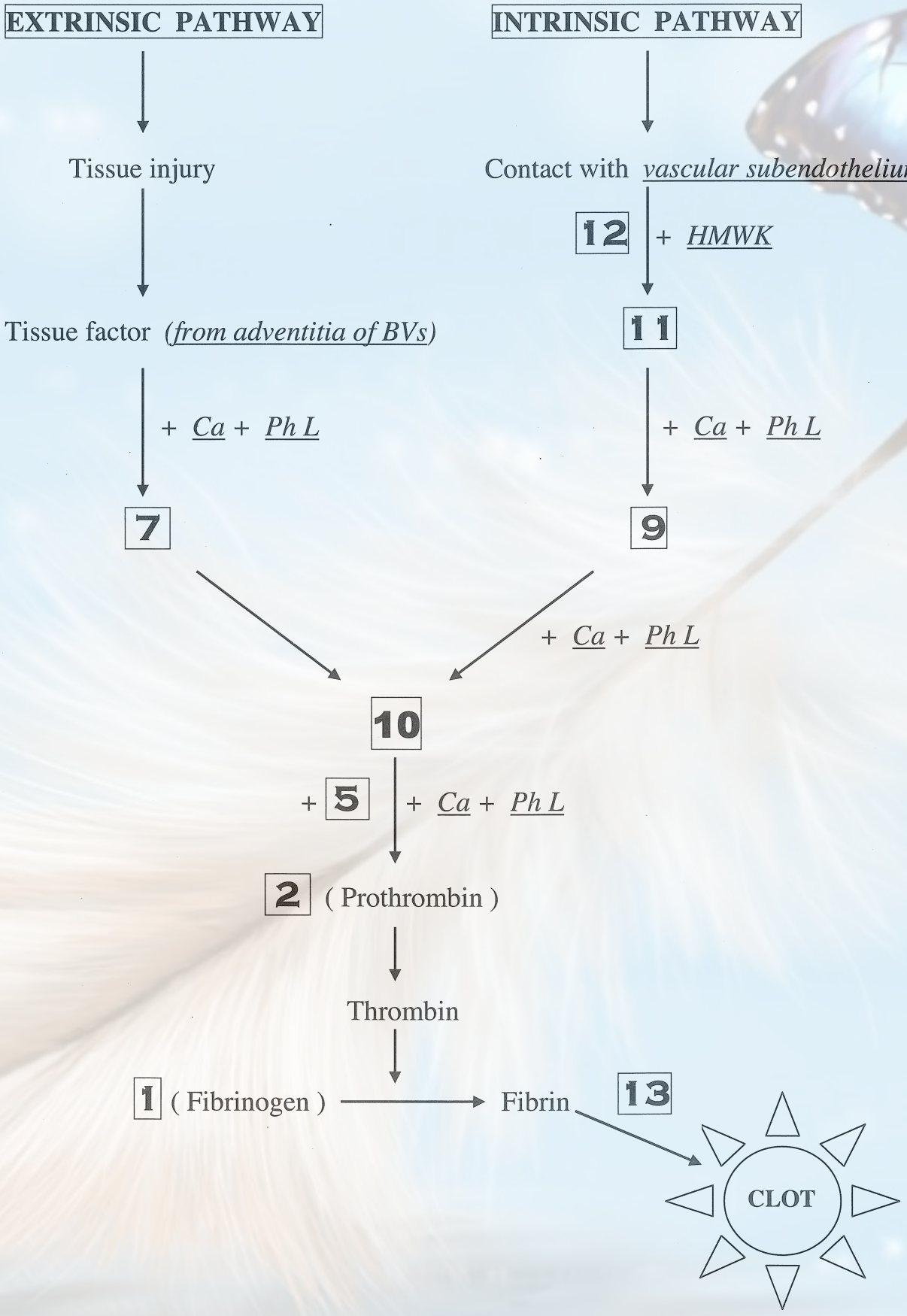
3. COAGULATION SYSTEM: " SECONDARY HEMOSTASIS "

- It requires several MINUTES for completion & involves **2 pathways**:

- *Intrinsic pathway.*
- *Extrinsic pathway.*

} ⟶ **Fibrin clot**

COAGULATION PATHWAYS



GENERAL TESTS FOR HEMOSTASIS

1. BLEEDING TIME — BT — (2 – 7 minutes)

- Normally: It measures platelet plug formation.
- Prolonged: Diseases affecting the PLATELETS:
  - o *Thromboctopenia* " *Decreased platelets* ".
  - o *Thromboctopathy* " *Diseased platelets* ".

2. COAGULATION TIME — CT — (5 – 10 minutes)

- Normally: It measures coagulation function (coagulation factors).
- Prolonged: All types of COAGULATION disorders.

3. PROTHROMBIN TIME — PT — (12 – 14 seconds)

- Normally: It measures the function of the **ex**trinsic & common pathways.
  It is measured by: adding **Tissue factor** + *Ca* + *Ph L* to the plasma and measuring the time to clot formation.
- Prolonged: Diseases of both the **ex**trinsic & common pathways:
  - o *Diminished factors:* **7, 10, 5, 2, 1.**
  - o *Liver cell failure.*
  - o *Vitamin K deficiency* (OJ, **oral anticoag, malabsorption syndrome).**

4. ACTIVATED PARTIAL THROMBOPLASTIN TIME — APTT — (30 – 40 seconds)

- Normally: It measures the function of the **in**trinsic & common pathways.
  It is measured by: adding **Kaolin** + *Ca* + *Ph L* to the plasma and measuring the time to clot formation.
- Prolonged: Diseases of both the **in**trinsic & common pathways:
  - o *Diminished factors:* **12, 11, 9, 8, 10, 5, 2, 1.**

5. THROMBIN TIME — TT — (9 – 11 seconds)

- Normally: It measures the ability to convert Fibrinogen to Fibrin.
  It is measured by: adding **Thrombin** to the plasma and measuring the time to clot formation.
- Prolonged: Diseases affecting FIBRINOGEN:
  - o *Fibrinogen deficiency* *(afibrinogenemia).*
  - o *Fibrinogen dysfunction* *(dysfibrinogenemia).*
  - o *Fibrinogen inhibitors* *(patients on heparin).*
  - o *DIC.*

HEMOSTATIC DISORDERS

TYPES

I. PURPURA

- Bleeding tendency due to defects in **PLATELETS** or in **VESSEL WALL**.

II. COAGULOPATHY

- Bleeding tendency due to defects in **COAGULATION FACTORS**.

I. PURPURA

A) PLATELET DEFECT

1. Thrombocytopenia: " Decreased platelets "

a) Decreased platelet production:

- **B**one marrow failure.
- **B**one marrow infiltration.
- **M**egaloblastic anemia.
- **M**yelodysplastic syndromes.
- *PAROXYSMAL NOCTURNAL HEMOGLOBINURIA.*

b) Increased platelet destruction:

- Autoimmune: **Primary** (*ITP*), **Secondary** (*SLE*, *CLL*, *Lymphoma*, *drugs* as α-meth-d).
- Acute infections.
- Hypersplenism.
- DIC, TTP, HUS.

2. Thrombocytopathy: " Diseased platelets "

a) Hereditary: *e.g. Glanzmann's disease.*

b) Acquired:

- Uremia.
- Multiple myeloma.
- Thrombocytosis.
- Antiplatelet drugs: *aspirin*, *dipyridamole*, *ticlopidine*, *clopidogrel*.
- Autoimmune: *SLE*.

B) VESSEL WALL DEFECT (Vascular Purpura)

- **I**mmune: Vasculitis e.g. *SLE, PAN, Henoch-Schonlein purpura.*
- **I**nfection: *SBE, meningococcemia.*
- **I**atrogenic: *Salicylates, Sulphonamides, Penicillins, Corticosteroids.*
- **I**diopathic: *Purpura simplex.*
- **S**curvy.
- **S**enile purpura.
- **C**ushing's syndrome.
- **C**ongenital: *Ehlers-Danlos syndrome.*

II. COAGULOPATHY

A) HEREDITARY

- Hemophilia.
- Fibrinogen defect: *Afibrinogenemia, Dysfibrinogenemia.*

B) ACQUIRED

- Liver **failure**.
- Renal **failure**.
- **D**eficiency of vitamin K.
- **D**IC.
- **D**rugs: *Heparin, oral anticoagulants, fibrinolytic agents.*

CLINICAL PICTURE

I. BLEEDING:

A) In Purpura:

1. Site of bleeding:
   - Orificial: *epistaxis, melena, **H**ematochezia, **H**ematemesis, **H**emoptysis, **H**ematuria.*
   - Cutaneous: *petichae, ecchymosis, excessive bleeding from wounds, **+ ve Hess test**.*
   - MM: *oral, gingival, conjunctival.*
   - Internal: ***intracranial hge, retinal hge, cavitary hge** (serous membranes).*
2. Mechanism of bleeding:
   - Bleeding: *spontaneous* or *post-traumatic.*
3. Character of bleeding:
   - Bleeding: *immediate.*

B) In Coagulopathy:

1. Site of bleeding:
   - Orificial: *epistaxis, melena, **H**ematochezia, **H**ematemesis, **H**emoptysis, **H**ematuria.*
   - Cutaneous: *petichae, ecchymosis, excessive bleeding from wounds, **- ve Hess test**.*
   - MM: *oral, gingival, conjunctival.*
   - Internal: ***hemarthrosis**, **muscle hematoma**, **others like in purpura**.*
2. Mechanism of bleeding:
   - Bleeding: *spontaneous* or *post-traumatic.*
3. Character of bleeding:
   - Bleeding: *delayed.*

II. ANEMIA:

- Acute & chronic post-hemorrhagic anemia may occur.

III. SHOCK:

- Severe hemorrhage may lead to: *hypovolemia* & *shock.*

IV. MANIFESTATIONS OF THE CAUSE.

Hess test (capillary fragility test)

Method: A circle 5 cm in diameter is marked on the antecubital fossa. The Sphygmomanometer is inflated to midway between SBP & DBP for 5 minutes. Count the number of petichae within the circle.

Result: Positive test means the presence of more than 10 petichae.

Value: It is POSITIVE in all cases of purpura

INVESTIGATIONS

A) Screening investigations:

- GENERAL TESTS FOR HEMOSTASIS.

B) Specific investigations:

1. PLATELETS:
   - Platelet count: Decreased in thrombocytopenia.
   - Platelet function tests: to estimate platelet aggregation.
2. CBC:
   - May detect the cause of thrombocytopenia (e.g. leukemia).
3. BM examination:
   - May detect the cause of thrombocytopenia (e.g. aplastic anemia).
4. ASSAY:
   - Coagulation factors assay, FDPs assay.

IDIOPATHIC THROMBOCYTOPENIC PURPURA

ETIOLOGY

- Autoimmune disease in which **antiplatelet antibodies** (usually IgG) are present.
- These autoantibodies directed against glycoprotein IIb / IIIa of the platelets, will sensitize the platelets resulting in their premature removal from the circulation by macrophages of the RES, especially the SPLEEN.
- The life span of platelets is reduced to few hours (*normally: 7 days*).

CLINICAL TYPES "*2 types*"

I. ACUTE ITP

Age: children.
Sex: equal.
Onset: acute.
Course:
- 90 %: **resolve** spontaneously within 2 weeks to 6 months.
- 10 %: develop **chronic** ITP (lasting > 6 months).

CP: see before.

Investigations:
- Platelets: markedly ↓↓ (usually below 20,000 / cmm).
- BT: prolonged.
- CT: normal.
- PT: normal.
- APTT: normal.
- TT normal.
- BM examination: increased number & size of megakaryocytes with: "**defective budding**".
- Antiplatelet antibodies: Antiglycoprotein IIb / IIIa antibodies are detected.

Treatment:

1. **General measures:**
   - **Avoid:** *trauma, invasive procedures, antiplatelets.*
2. **Specific measures:**
   - **Prednisone:** 1 mg / Kg / day.
   - **Platelet transfusion:** in cases of severe hemorrhage.
   - **IV gamma globulins.**

II. CHRONIC ITP

Age: yoyng adults & middle age.

Sex: more common in females.

Onset: gradual.

Course:

- Prolonged for: ***months*** or ***years*** with remissions & exacerbations.

CP: see before.

Investigations:

- Platelets: moderately ↓↓ (usually 20,000 – 100,00 / cmm).
- BT: prolonged.
- CT: normal.

- PT: normal.
- APTT: normal.
- TT normal.

- BM examination: increased number & size of megakaryocytes with: " **defective budding** ".

- Antiplatelet antibodies: Antiglycoprotein IIb / IIIa antibodies are detected.

Treatment:

1. **General measures:**
   - **Avoid:** *trauma, invasive procedures, antiplatelets.*
2. **Specific measures:**
   - **Prednisone:** 1 mg / Kg / day.
   - *If no response:* *splenectomy.*
   - *If no response:*
     - *Immunosuppressives:* *Cyclophosphamide or Cyclosporin.*
     - *Danazol.*
   - **Platelet transfusion:** in cases of severe hemorrhage.
   - **IV gamma globulins.**

HEMOPHILIA

ETIOLOGY

- It is a hereditary deficiency of AHG (factor VIII) transmitted as X-linked from: healthy female carriers to their **male offsprings**.

CLINICAL PICTURE

Age:	since birth.
Sex:	males.
Family history:	positive.
CP:	see before.

INVESTIGATIONS

1. CT: prolonged.
2. APTT: prolonged.
3. TT: normal.
4. PT: normal.
5. BT: normal.
6. Platelet count: normal.
7. Serum AHG: markedly decreased.

TREATMENT

1. **General measures:** **avoid:** *trauma, invasive procedures, antiplatelets.*
2. **Specific measures:** " ttt of bleeding episodes "
   - Factor VIII replacement: *factor VIII concentrates, fresh frozen plasma.*
   - Fresh blood transfusion: *in cases of severe hemorrhage.*
   - Local pressure.
   - For hemathrosis: *immobilization, elastic bandage, analgesics, physiotherapy.*

	Purpura	Hemophilia
1. FH	Negative	Positive
2. Sex	Females	Males
3. Age	Any age	Since birth
4. Relation to trauma	Immediate	Delayed
5. Hemarthrosis	Uncommon	Common
6. Hess test	Positive	Negative
7. INVESTIGATIONS • BT • CT • APTT • Platelets	 • Prolonged • Normal • Normal • Low	 • Normal • Prolonged • Prolonged • Normal

Hypoprothrombinemia

ETIOLOGY

1. Liver cell failure.
2. Vitamin K deficiency: *OJ, Oral anticoagulants, Malabsorption syndrome.*
3. Hereditary deficiency of prothrombin: RARE.

CLINICAL PRESENTATION

- Bleeding tendency: especially *post-traumatic*.
- CP of the cause: most important features of each cause.
  e.g. *Features of liver cell failure*.

INVESTIGATIONS

1. APTT is prolonged.
2. PT is prolonged & improves by parentral vitamin K *in cases of vitamin K deficiency ONLY*.
   PT is prolonged but does not improve by parentral vitamin K *in cases of liver cell failure*.
3. TT is normal.
4. Investigations for the cause: most important investigations of each cause.
   e.g. *Hypoalbuminemia in liver cell failure*.

TREATMENT

1. Transfusion of: *fresh frozen plasma.*
2. Treatment of: *the cause*: e.g. ttt of liver cell failure.
3. Treatment with: parentral vitamin K *in cases of vitamin K deficiency*.

HENOCH-SCHONLEIN PURPURA

ETIOLOGY

- It usually follows a: STREPTOCOCCAL INFECTION.
- It usually affects: CHILDREN.

CLINICAL PICTURE

1. Blood: Purpura.
2. Joints: Arthralgias.
3. GIT: Abdominal colics, Melena, Hematochezia.
4. Renal: Hematuria, GN, Renal failure.

TREATMENT

- Corticosteroids: prednisone 1 mg / Kg / day orally.

THROMBOCYTOSIS

MPD

1. ESSENTIAL THROMBOCYTOSIS " PRIMARY "

A) It is a myeloproliferative disorder (Blood malignancy) characterized by:
" Excessive proliferation of "
MEGAKARYOCYTES in BM → ↑↑ Platelets in the peripheral blood.

B) It also occurs in other forms of MPD: *CML, PRV, Idiopathic myelofibrosis.*

CLINICAL PICTURE

1. THROMBOSIS.
2. BLEEDING.
3. SPLENOMEGALY: HUGE size.

INVESTIGATIONS

1. Platelet count: persistently greater than **1,000,000 / cmm.**
2. Bone marrow: marked Hypercellularity of **Megakaryocytes.**

TREATMENT

1. Chemotherapy: Hydroxyurea, Radioactive phosphorus.
2. Symptomatic ttt: Platelet-pheresis.

2. REACTIVE THROMBOCYTOSIS " SECONDARY "

- It is more common than essential thrombocytosis.
- Causes include:
    - *Inflammation.*
    - *Infection.*
    - *Malignancy.*
    - *Hemorrhage.*
    - *POST – SPLENECTOMY.*

THROMBOPHILIA (Hypercoagulability)

Thrombophilia is the tendency to develop thrombosis (blood clots) due to an abnormality in the system of coagulation.

CAUSES

I. Congenital:

- Homocysteinemia.
- Factor V Leiden.
- Prothrombin mutation.
- Deficiency of: protein C, protein S, Antithrombin III.

II. Acquired:

- Homocysteinemia.
- Antiphospholipid syndrome.
- SLE.
- PNH.
- DIC.
- Myeloproliferative disorders.
- Malignancy.
- Nephrotic syndrome.
- IATROGENIC:
  - *CCPs.*
  - *Heparin – induced thrombocytopenia.*

DISSEMINATED INTRAVASCULAR COAGULATION

DIC

DEFINITION

- Abnormal activation of coagulation → excessive THROMBOSIS in the circulation.
- CONSUMPTION of platelets & clotting factors occurs.
- Thrombosis → secondary activation of Fibrinolysis → ↑ FDPs → excessive BLEEDING.

ETIOLOGY

1. Septicemia.
2. Severe: shock, burns, trauma.
3. Severe: hemolytic transfusion reactions.
4. **Advanced** obstetric complications: *abruptio placenta*, *eclampsia*.
5. **Advanced** malignancy.

CLINICAL PICTURE

1. Extensive BLEEDING.
2. Associated Multiple organ failure: *ARF*, *ARDS*, *SEPSIS*.
3. Associated Hemolytic anemia: microangiopathic.
4. THROMBOTIC events: especially **skin** & **kidneys**.

INVESTIGATIONS

1. BT, CT, PT, APTT, TT: prolonged.
2. Platelet count: decreased.
3. Fibrinogen level: decreased markedly.
4. **FDPs:** **HIGH LEVELS.**

TREATMENT

1. TTT of the cause.
2. For BLEEDING: Platelet transfusion, Fresh frozen plasma.
3. For THROMBOSIS: Heparin may be used to prevent intravascular clotting.

CAUSES OF SPLENOMEGALY

I. INFECTIONS

1. **Viral:** *IMN, HIV, Viral hepatitis.*
2. **Bacterial:**
   - SBE.
   - Septicemia.
   - Brucellosis.
   - Typhoid.
   - TB: *Miliary TB.*
3. **Parasitic:**
   - Malaria.
   - Schistosomiasis.
   - Toxoplasmosis.
   - Kala-azar.
4. **Mycoplasma, Fungi, Rickettsiae.**

II. CONGESTIVE SPLENOMEGALY

1. All causes of portal hypertension.
2. Splenic vein occlusion.

III. HEMATOLOGIC

1. Anemias: *Hemolytic, megaloblastic, iron deficiency.*
2. Immune cytopenias: *AIHA.*
3. Blood malignancies: *Leukemias, Lymphomas, MPD.*

IV. NEOPLASTIC

1. Blood malignancies.
2. Primary splenic tumours: *Lymphangiosarcoma.*

V. INFILTRATION

1. Lipid storage diseases.
2. Amyloidosis.

VI. INFLAMMATION

1. Collagen diseases: *SLE, Felty's syndrome, Still's disease.*
2. Sarcoidosis.

VII. ENDOCRINE

1. Acromegaly.
2. Grave's disease.

VIII. SPLENIC ABSCESS & CYST.

CAUSES OF HUGE SPLENOMEGALY

1. **Severe portal hypertension:** *especially Schistosomiasis.*
2. **Infections:** *Chronic malaria, Kala-azar.*
3. **Hematologic:** *Thalassemia major.*
4. **MPD:** *CML, PRV, Essential thrombocythemia, Idiopathic Myelofibrosis.*
5. **Neoplastic:** *Lymphomas, Hairy cell leukemia.*
6. **Infiltration:** *Amyloidosis, Gaucher's disease.*
7. **Inflammation:** *Sarcoidosis, Felty's syndrome.*

HYPERSPLENISM

DEFINITION

- Exaggeration of the normal splenic function → destruction of one or more of the blood cells:
  " Monocytopenia, or Bicytopenia, or Pancytopenia ".

ETIOLOGY

1. Secondary: Splenomegaly.
2. Idiopathic: Rare.

CLINICAL PICTURE

1. One or more of the following:
   - Anemia: RBCs.
   - Bleeding: PLATELETS.
   - Fever & recurrent infections: WBCs.
2. Splenomegaly: + features of the cause of splenomegaly.

INVESTIGATIONS

1. **CBC:** One or more of the following:
   - RBCs: Normocytic normochromic anemia, with ***reticulocytosis***.
   - PLATELETS: Thrombocytopenia.
   - WBCs: Leukopenia.
2. **Bone marrow examination:** Hyperplasia.
3. **Cr. Labeled RBCs:** excessive destruction in the spleen.
4. **Investigations for the cause of splenomegaly.**

TREATMENT

1. SPLENECTOMY.
2. Symptomatic ttt: *for anemia, bleeding, infections.*
3. TTT of the cause.

LYMPHOMAS

DEFINITION

- Neoplasms of the IMMUNE SYSTEM **(B or T lymphocytes)** usually arising in the LN.
- They are classified according to HISTOLOGY into:
  - Hodgkin's disease (HD).
  - Non-Hodgkin's lymphoma (NHL).

ETIOLOGY

1. The Rule: UNKNOWN.
2. The Exception: associated with: **I**nfection **(EBV)**, **I**rradiation, **I**mmunodeficiency.

CLINICAL PICTURE

I. LYMPHATIC MANIFESTATIONS

1. LYMPHADENOPATHY

A. LN ENLARGEMENT

- In HD: **Discrete,** rubbery, painless, nontender.
  Localized at the onset, then become generalized.
- In NHL: **Amalgamated,** rubbery, painless, nontender.
  Generalized at the onset.

B. PRESSURE MANIFESTATIONS

- Mediastinal syndrome, Obstructive jaundice.

2. SPLENOMEGALY

- May reach a HUGE size.

II. EXTRA-LYMPHATIC MANIFESTATIONS

1. GENERAL

- **F**ever: "Pel-Ebstein in HD"
  Fever for 1-2 weeks alternating with No fever for 1-2 weeks.
- **F**atigue: + loss of weight + night sweats.

2. ABDOMINAL

- Liver: Hepatomegaly & jaundice.
- GIT: Bleeding & malabsorption.

3. CHEST

- Lung: Infiltration.
- Pleura: Effusion.

4. NEUROLOGICAL

- Focal spinal manifestations: *e.g. paraplegia.*
- Focal cerebral manifestations: *e.g. hemiplegia.*

5. SKIN

- Pruritus.
- Nodules.
- Hyperpigmentation.

6. SKELETAL

- **P**ains: bony.
- **P**athological fractures.

7. IMMUNOLOGICAL

- Immunodeficiency → Opportunistic infections: *HZ, Fungi.*
- Immune cytopenias → AIHA, Autoimmune thrombocytopenia.

INVESTIGATIONS

1. BIOPSY (LN, BM) *" The most important investigation "*

- In HD: The histological hallmark is: " Reed Sterberg cell ".
- In HD: The histological classification is: " 4 types ":
  - *Lymphocyte predominance:* *many Lymphocytes,* *few RS cells.*
  - *Lymphocyte depletion:* *few Lymphocytes,* *many RS cells.*
  - *Mixed cellularity.*
  - *Nodular sclerosis:* *excessive fibrosis.*

2. BLOOD PICTURE

- WBCs: Leukocytosis, Lymphocytosis.
- RBCs: Anemia (AIHA or Myelophthisic).
- PLATELETS: Thrombocytopenia (Autoimmune).
- ESR: Elevated.

3. IMAGING

- ABDOMEN: Abdominal ultrasonography & CT.
- CHEST: CXR & CT.

4. STAGING LAPAROTOMY.

CLINICAL STAGING OF LYMPHOMAS

I. Single LN region or Single extralymphatic site.

II. Two or more LN regions on the **same side** of the diaphragm.

III. LN regions on **both sides** of the diaphragm.

IV. Diffuse extralymphatic sites.

A = **A**bsence of systemic symptoms.

B = **P**resence of systemic symptoms (*fever, weight loss, night sweats*).

TREATMENT

1. RADIOTHERAPY

- Stages: I or II A.
- Severe pressure manifestations: e.g. focal spinal cord compression.

2. CHEMOTHERAPY

- Stages: II B, III, IV.

In HD: ***MOPP*** (***M****echlorethamine,* ***O****ncovin,* ***P****rocarbazine,* ***P****rednisone*).

In NHL: *Cyclophosphamide, Doxorubicin, Oncovin, Prednisone.*

GENERALIZED LYMPHADENOPATHY

INFECTIONS

1. VIRAL: IMN, AIDS, Viral hepatitis.
2. BACTERIAL: Brucellosis, TB, Secondary Syphilis.
3. PROTOZOAL: Toxoplasmosis.
4. FUNGAL: Histoplasmosis.

NEOPLASTIC

1. BLOOD MALIGNANCIES: Lymphomas, Leukemias, MM.
2. SOLID MALIGNANCIES: Metastatic carcinoma.

IMMUNOLOGICAL

1. **S**LE, Felty's syndrome.
2. **S**ARCOIDOSIS.

METABOLIC

1. AMYLOIDOSIS.
2. LIPID STORAGE DISEASES.

رقم الإيداع :٢٤٤٠٥ / ٢٠٠٨

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